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suki-shi, Osaka 569-1032 (JP). YAMANE, Taihei [JP/JP];  
10-6-203, Tsukimigaoka, Nigawa, Takarazuka-shi, Hyogo  
665-0067 (JP).

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(74) Agent: TAKASHIMA, Hajime; Fujimura Yamato Seimei  
Bldg., 2-14, Fushimimachi 4-chome, Chuo-ku, Osaka-shi,  
Osaka 541-0044 (JP).

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2001-382232 14 December 2001 (14.12.2001) JP(71) Applicant (for all designated States except US): TAKEDA  
CHEMICAL INDUSTRIES, LTD. [JP/JP]; 1-1,  
Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka  
541-0045 (JP).

(72) Inventors; and

(75) Inventors/Applicants (for US only): OI, Satoru  
[JP/JP]; 7-10-509, Ayameikeminami 1-chome, Nara-shi,  
Nara 631-0033 (JP). IKEDOU, Koji [JP/JP]; 6-4,  
Besshochokobayashi, Himeji-shi, Hyogo 671-0222 (JP).  
TAKEUCHI, Koji [JP/JP]; 50-B-204, Yamadaminami,  
Suita-shi, Osaka 565-0823 (JP). OGINO, Masaki [JP/JP];  
15-13, Kamino-cho, Nishinomiya-shi, Hyogo 663-8021  
(JP). BANNO, Yoshihiro [JP/JP]; 17-17-202, Meish-  
incho, Takatsuki-shi, Osaka 569-1128 (JP). TAWADA,(81) Designated States (national): AE, AG, AL, AM, AT, AU,  
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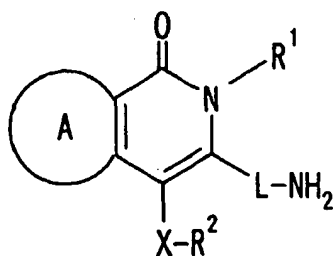
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(54) Title: FUSED HETEROCYCLIC COMPOUNDS



(1)

agent for the prophylaxis or treatment of diabetes and the like.

(57) Abstract: The present invention provides a compound of  
the formula: wherein ring A is an optionally substituted 5 to  
10-membered aromatic ring; R<sup>1</sup> and R<sup>2</sup> are the same or different  
and each is an optionally substituted hydrocarbon group or an  
optionally substituted heterocyclic group; X is a bond and the  
like; and L is a divalent hydrocarbon group, and a salt thereof,  
except 3-(aminomethyl)-2,6,7-trimethyl-4-phenyl-1(2H)-iso-  
quinolinone, 3-(aminomethyl)-2-methyl-4-phenyl-1(2H)-iso-  
quinolinone, 3-(aminomethyl)-6-chloro-2-methyl-4-  
phenyl-1(2H)-isoquinolinone and 3-(aminomethyl)-2-iso-  
propyl-4-phenyl-1(2H)-isoquinolinone. The compound shows  
a superior peptidase-inhibitory activity and is useful as an

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*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

**DESCRIPTION**  
**FUSED HETEROCYCLIC COMPOUNDS**

**TECHNICAL FIELD**

The present invention relates to a novel fused  
5 heterocyclic compound having a peptidase (preferably  
dipeptidyl dipeptidase IV) inhibitory activity, which is  
useful as a prophylactic or therapeutic agent of  
diabetes and the like.

**BACKGROUND ART**

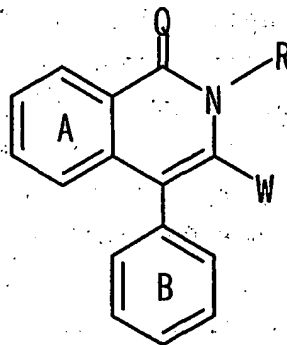
10 Peptidase is known to relate to various diseases.  
Dipeptidyl dipeptidase IV (hereinafter sometimes to be  
abbreviated as DPP-IV), which is one kind of peptidases,  
is serine protease that specifically binds with a  
peptide containing proline (or alanine) at the 2nd from  
15 the N terminal and cleaves the C-terminal side of the  
proline (or alanine) to produce dipeptide. DPP-IV has  
been shown to be the same molecule as CD26, and reported  
to be also involved in the immune system. While the  
role of DPP-IV in mammals has not been entirely  
20 clarified, it is considered to play an important role in  
the metabolism of neuropeptides, activation of T cells,  
adhesion of cancerous cells to endothelial cells,  
invasion of HIV into cells and the like. Particularly,  
from the aspect of glycometabolism, DPP-IV is involved  
25 in the inactivation of GLP-1 (glucagon-like peptide-1)  
and GIP (Gastric inhibitory peptide/Glucose-dependent  
insulinotropic peptide), which are incretins. With  
regard to GLP-1, moreover, its half-life in plasma is as  
short as 1-2 minutes, and GLP-1 is known to be degraded  
30 by DPP-IV and markedly lose its physiological activity  
because GLP-1(9-36)amide, which is a degradation product  
by DPP-IV, acts on GLP-1 receptor as an antagonist. It  
is also known that suppression of degradation of GLP-1  
by inhibiting activity of DPP-IV leads to potentiation  
35 of physiological activity that GLP-1 shows, such as  
glucose concentration-dependent insulinotropic effect

and the like. From these facts, a compound having a DPP-IV inhibitory activity is expected to show effect on impaired glucose tolerance, postprandial hyperglycemia and fasting hyperglycemia observed in type I and type II diabetes and the like, , obesity or diabetic complications associated therewith and the like.

As therapeutic agents of diabetes now in use, a sulfonylurea, a biguanide, an  $\alpha$ -glucosidase inhibitor and the like are known. While a sulfonylurea produce a potent hypoglycemic action, it sometimes causes serious hypoglycemia and requires attention during use. A biguanide easily causes lactic acidosis which is a relatively serious side effect. An  $\alpha$ -glucosidase inhibitor delays digestion and absorption of glucose in the gastrointestinal tract and suppresses increase in the blood glucose level after meal, but side effects of sense of distension, diarrhea and the like are problematic (JOSLIN'S DIABETES MELLITUS 13Th Edition 521-522).

Isoquinolone compounds are described in the following publications.

(1) JP-A-7-76573 describes a compound of the formula

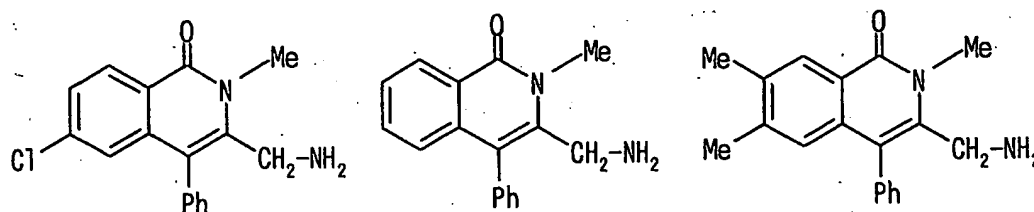


wherein ring A and ring B are optionally substituted benzene rings; Q is an oxygen atom or a sulfur atom; R is a hydrogen atom, an optionally substituted hydrocarbon group and the like; W is  $-\text{CH}_2\text{OH}$ ,  $-\text{CH}_2\text{NHR}^1$ , -

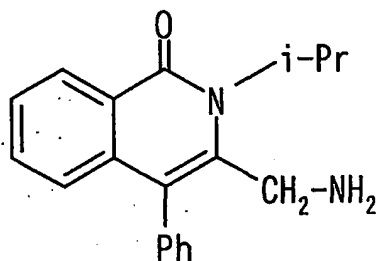


$\text{CH}_2\text{CH}_2\text{NHR}^1$  ( $\text{R}^1$  is hydrogen atom or optionally substituted hydrocarbon group) and the like, as a starting material compound of a compound having a calcium antagonistic action and the like, wherein the specific examples are

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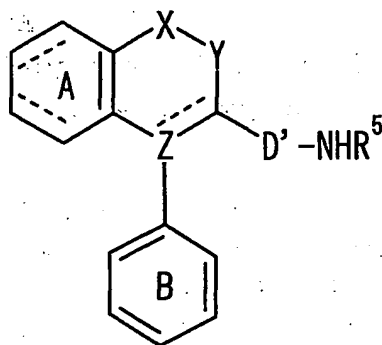
(2) Archiv der Pharmazie, vol. 324, pp. 809-814 (1991) describes a compound of the formula



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as a starting material compound of a compound having an anticonvulsant action.

(3) JP-A-7-10844 describes a compound of the formula



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wherein ring A is optionally substituted; ring B is an optionally substituted benzene ring; one of X and Y is -

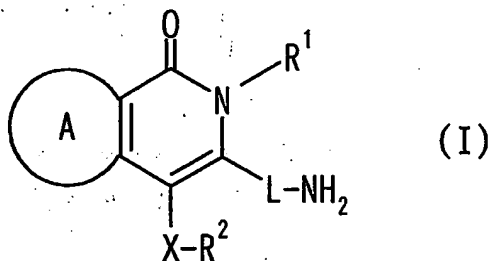
NR<sup>1</sup>- (R<sup>1</sup> is a hydrogen atom, an optionally substituted hydrocarbon group and the like), -O- or -S-, the other is -CO-, -CS- and the like; ----- is a single bond or a double bond; Z is a carbon atom and the like; D' is a C<sub>1</sub>-  
 5 alkylene group; and R<sup>5</sup> is a hydrogen atom or an optionally substituted hydrocarbon group] as a starting material compound of a compound having an acyl-CoA cholesterol acyl transferase (ACAT) inhibitory action and the like.

10 However, there is no report showing that these compounds have a peptidase (preferably DPP-IV) inhibitory activity.

There is a demand on the development of a compound having a peptidase (preferably DPP-IV) inhibitory  
 15 activity, useful as a prophylactic or therapeutic drug of diabetes and the like and having superior properties in terms of efficacy, duration of action, specificity, low toxicity and the like.

#### SUMMARY OF THE INVENTION

20 The present inventors have first found that a compound of the formula



wherein

ring A is an optionally substituted 5 to 10-  
 25 membered aromatic ring;

R<sup>1</sup> and R<sup>2</sup> are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

30 X is a bond, -O-, -S-, -SO-, -SO<sub>2</sub>- or -NR<sup>3</sup>-

(R<sup>3</sup> is a hydrogen atom or an optionally substituted hydrocarbon group); and

L is a divalent hydrocarbon group, and a salt thereof,

5 which are characterized by the chemical structure where an amino group is bonded to a fused heterocycle via a divalent hydrocarbon group, have a superior peptidase (preferably DPP-IV) inhibitory activity and are useful as a prophylactic or therapeutic  
10 agent of diabetes and the like. Based on this finding, the present inventors have conducted intensive studies and completed the present invention.

Accordingly, the present invention relates to:

- 1) a compound of the formula (I) or a salt thereof  
15 except 3-(aminomethyl)-2,6,7-trimethyl-4-phenyl-1(2H)-isoquinolinone, 3-(aminomethyl)-2-methyl-4-phenyl-1(2H)-isoquinolinone, 3-(aminomethyl)-6-chloro-2-methyl-4-phenyl-1(2H)-isoquinolinone and 3-(aminomethyl)-2-isopropyl-4-phenyl-1(2H)-isoquinolinone,
- 20 2) the compound of 1), wherein the 5 to 10-membered aromatic ring for ring A is a benzene ring,
- 3) the compound of 1), wherein the ring A is a 5 to 10-membered aromatic ring optionally having 1 to 3 substituent(s) selected from
  - 25 a) a halogen atom,
  - b) a nitro group,
  - c) a cyano group,
  - d) a C<sub>1-3</sub> alkylendioxy group,
  - e) a C<sub>1-10</sub> alkyl group or a C<sub>2-10</sub> alkenyl group, each
- 30 optionally having 1 to 3 substituent(s) selected from a halogen atom, a hydroxy group, a carboxyl group, an alkoxy carbonyl group having 2 to 8 carbon atoms, a carbamoyl group, a cyano group, an amino group, an alkanoylamino group having 2 to 8 carbon atoms, an  
35 alkoxy carbonylamino group having 2 to 8 carbon atoms, an alkylsulfonylamino group having 1 to 8 carbon atoms,

- f) an optionally substituted hydroxy group,
- g) an acyl group,
- h) an optionally substituted amino group,
- i) an aryl group having 6 to 14 carbon atoms,
- 5 j) an optionally substituted thiol group, and
- k) an optionally substituted heterocyclic group,
- 4) the compound of 1), wherein  $R^1$  is an alkyl group having 1 to 10 carbon atom(s),
- 5) the compound of 1), wherein  $R^1$  is an alkyl group
- 10 having 4 to 10 carbon atoms,
- 6) the compound of 1), wherein X is a bond or -O-,
- 7) the compound of 1), wherein the divalent hydrocarbon group for L is an alkylene group having 1 to 10 carbon atom(s),
- 15 8) the compound of 1), wherein  $R^2$  is an optionally substituted hydrocarbon group,
- 9) the compound of 1), wherein  $R^2$  is an alkyl group having 1 to 10 carbon atom(s), an aryl group having 6 to 14 carbon atoms or an aralkyl group having 7 to 13
- 20 carbon atoms, each optionally having 1 to 3 substituent(s) selected from halogen atom, hydroxy group, nitro group, amino group, optionally halogenated alkyl group having 1 to 6 carbon atom(s), alkoxy group having 1 to 6 carbon atom(s), aromatic heterocyclic group and
- 25 cycloalkyl group having 3 to 10 carbon atoms,
- 10) the compound of 1), which is 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carbonitrile,
- 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-
- 30 dihydro-6-isoquinolyl]-1,3-thiazole-4-carboxylic acid,
- 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carboxamide,
- ethyl 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carboxylate,
- 35 (E)-3-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-2-propenamide,

- (E)-3-[3-(aminomethyl)-2-isobutyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]-2-propenamide,  
3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxamide,  
5 2-[[3-(aminomethyl)-2-isobutyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]oxy]acetamide,  
or a salt thereof,  
11) a crystal of 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-  
10 carbonitrile or a salt thereof,  
12) a crystal of 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carboxamide or a salt thereof,  
13) a crystal of 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-  
15 1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carboxamide or a salt thereof,  
14) a crystal of ethyl 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carboxylate or a salt thereof,  
20 15) a crystal of (E)-3-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-2-propenamide or a salt thereof,  
16) a crystal of (E)-3-[3-(aminomethyl)-2-isobutyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]-2-propenamide or  
25 a salt thereof,  
17) a crystal of 3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxamide or a salt thereof,  
18) a crystal of 2-[[3-(aminomethyl)-2-isobutyl-4-  
30 phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]oxy]acetamide or a salt thereof,  
19) a pharmaceutical agent containing a compound of the formula (I) or a salt thereof,  
20) a pharmaceutical agent comprising the pharmaceutical  
35 agent of 19) above in combination with at least one member selected from an insulin preparation, an insulin

- sensitizer, an  $\alpha$ -glucosidase inhibitor, a biguanide and an insulin secretagogue,
- 21) an agent for prophylaxis or treatment of diabetes, which contains a compound of the formula (I), a salt thereof or a prodrug thereof,
- 22) an agent for prophylaxis or treatment of diabetic complications, which contains a compound of the formula (I), a salt thereof or a prodrug thereof,
- 23) an agent for prophylaxis or treatment of impaired glucose tolerance, which contains a compound of the formula (I), a salt thereof or a prodrug thereof,
- 24) an agent for prophylaxis or treatment of obesity, which contains a compound of the formula (I), a salt thereof or a prodrug thereof,
- 25) a peptidase inhibitor containing a compound of the formula (I), a salt thereof or a prodrug thereof,
- 26) the inhibitor of 25) above, wherein the peptidase is dipeptidyl dipeptidase IV,
- 27) a method of prophylaxis or treatment of diabetes in a mammal, which method comprising administering a compound of the formula (I), a salt thereof or a prodrug thereof to the mammal,
- 28) a method of prophylaxis or treatment of diabetic complications in a mammal, which method comprising administering a compound of the formula (I), a salt thereof or a prodrug thereof to the mammal,
- 29) a method of prophylaxis or treatment of impaired glucose tolerance in a mammal, which method comprising administering a compound of the formula (I), a salt thereof or a prodrug thereof to the mammal,
- 30) a method of prophylaxis or treatment of obesity in a mammal, which method comprising administering a compound of the formula (I), a salt thereof or a prodrug thereof to the mammal,
- 31) a method of inhibiting peptidase in a mammal, which method comprising administering a compound of the

formula (I), a salt thereof or a prodrug thereof to the mammal,

32) use of a compound of the formula (I), a salt thereof or a prodrug thereof for production of an agent for

5 prophylaxis or treatment of diabetes,

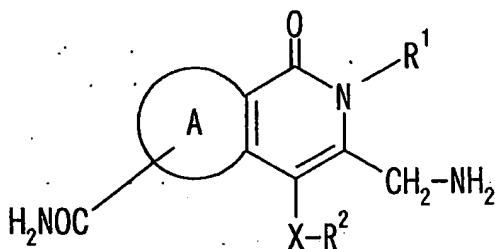
33) use of a compound of the formula (I), a salt thereof or a prodrug thereof for production of an agent for prophylaxis or treatment of diabetic complications,

34) use of a compound of the formula (I), a salt thereof  
10 or a prodrug thereof for production of an agent for prophylaxis or treatment of impaired glucose tolerance,

35) use of a compound of the formula (I), a salt thereof or a prodrug thereof for production of an agent for prophylaxis or treatment of obesity,

15 36) use of a compound of the formula (I), a salt thereof or a prodrug thereof for production of a peptidase inhibitor,

37) a production method of a compound of the formula



20 wherein

ring A

is a 5 to 10-membered aromatic ring;

R¹ and R²

are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

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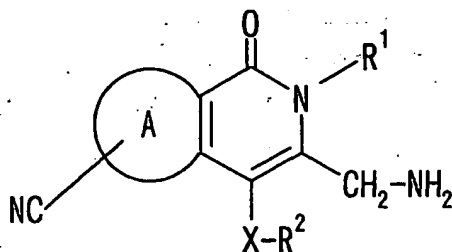
and

X

is a bond, -O-, -S-, -SO-, -SO₂- or -NR³- (R³ is a hydrogen atom or an optionally substituted hydrocarbon group),

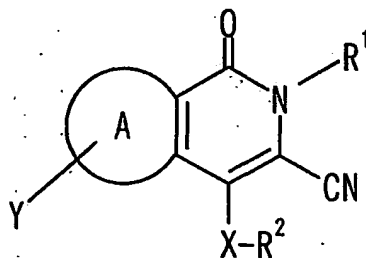
30 or a salt thereof, which method comprises subjecting a

compound of the formula



wherein the symbols are as defined above, or a salt thereof, to hydrolysis,

38) a compound of the formula



wherein

ring A is a 5 to 10-membered aromatic ring;

R<sup>1</sup> and R<sup>2</sup> are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

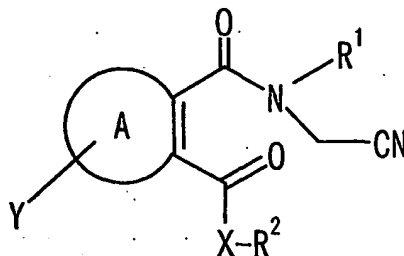
X is a bond, -O-, -S-, -SO-, -SO<sub>2</sub>- or -NR<sup>3</sup>- (R<sup>3</sup> is a hydrogen atom or an optionally substituted hydrocarbon group); and

Y is a halogen atom,

or a salt thereof,

39) a compound of the formula





wherein

ring A

R¹ and R²

is a 5 to 10-membered aromatic ring;  
are the same or different and each is an  
optionally substituted hydrocarbon group or  
an optionally substituted heterocyclic  
group;

X

is a bond, -O-, -S-, -SO-, -SO₂- or -NR³-  
(R³ is a hydrogen atom or an optionally  
substituted hydrocarbon group); and

Y

is a halogen atom,

or a salt thereof, and the like.

#### DETAILED DESCRIPTION OF THE INVENTION

Each symbol of the formula (I) is described in

detail in the following.

The "5 to 10-membered aromatic ring" of the  
"optionally substituted 5 to 10-membered aromatic ring"  
for ring A is, for example, a 5 to 10-membered aromatic  
hydrocarbon ring or a 5 to 10-membered aromatic  
heterocycle.

Preferable examples of the 5 to 10-membered  
aromatic hydrocarbon ring include benzene, naphthalene  
and the like.

Preferable examples of the 5 to 10-membered  
aromatic heterocycle include a 5 to 10-membered aromatic  
heterocycle containing 1 to 4 heteroatom(s) selected  
from an oxygen atom, a sulfur atom and a nitrogen atom  
as a ring-constituting atom, besides carbon atoms, such  
as furan, thiophene, pyrrole, oxazole, isoxazole,  
thiazole, isothiazole, imidazole, pyrazole, 1,2,3-

oxadiazole, furazan, 1,2,3-thiadiazole, 1,2,3-triazole, pyridine, pyridazine, pyrimidine, triazine, benzofuran, isobenzofuran, benzo[b]thiophene, indole, isoindole, 1H-indazole, benzimidazole, benzoxazole, 1,2-benzoisoxazole, 5 benzothiazole, 1,2-benzisothiazole, 1H-benzotriazole, quinoline, isoquinoline and the like.

The "5 to 10-membered aromatic ring" is preferably a benzene ring, a naphthalene ring, a thiophene ring, a pyridine ring and the like. Of these, a benzene ring is 10 preferable.

The "5 to 10-membered aromatic ring" optionally has 1 to 3 substituent(s) at substitutable position(s). Examples of the substituent include "halogen atom", "nitro group", "cyano group", "C<sub>1-3</sub> alkylenedioxy group", 15 "optionally substituted alkyl group having 1 to 10 carbon atom(s)", "optionally substituted alkenyl group having 2 to 10 carbon atoms", "optionally substituted alkynyl group having 2 to 10 carbon atoms", "optionally substituted cycloalkyl group having 3 to 10 carbon 20 atoms", "optionally substituted cycloalkenyl group having 3 to 10 carbon atoms", "optionally substituted cycloalkadienyl group having 4 to 10 carbon atoms", "optionally substituted aryl group having 6 to 14 carbon atoms", "optionally substituted heterocyclic group", 25 "acyl group", "optionally substituted amino group", "optionally substituted hydroxy group", "optionally substituted thiol group", "amidino group" and the like.

As the "halogen atom", for example, fluorine, chlorine, bromine, iodine and the like can be used, with 30 preference given to fluorine, chlorine and bromine.

Examples of the "C<sub>1-3</sub> alkylenedioxy group" include methylenedioxy, ethylenedioxy and the like.

As the "alkyl group having 1 to 10 carbon atom(s)" of the "optionally substituted alkyl group having 1 to 35 10 carbon atom(s)", for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, t.-butyl, pentyl,

isopentyl, neopentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, heptyl, octyl, nonyl, decyl and the like can be used.

5       As the "alkenyl group having 2 to 10 carbon atoms" of the "optionally substituted alkenyl group having 2 to 10 carbon atoms", for example, ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 3-hexenyl, 5-hexenyl, 1-heptenyl, 1-octenyl and the like  
10       can be used.

      As the "alkynyl group having 2 to 10 carbon atoms" of the "optionally substituted alkynyl group having 2 to  
15       10 carbon atoms", for example, ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-butyne, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-heptynyl, 1-octynyl and the like can be used.

20       The aforementioned "alkyl group having 1 to 10 carbon atom(s)", "alkenyl group having 2 to 10 carbon atoms" and "alkynyl group having 2 to 10 carbon atoms" optionally have 1 to 3 substituent(s) at substitutable position(s).

25       As these substituents, for example, cycloalkyl group having 3 to 10 carbon atoms, aryl group having 6 to 14 carbon atoms (e.g., phenyl, naphthyl and the like), aromatic heterocyclic group (e.g., thienyl, furyl, pyridyl, oxazolyl, thiazolyl, quinolyl and the like),  
30       non-aromatic heterocyclic group (e.g., tetrahydrofuryl, morpholino, thiomorpholino, piperidino, pyrroliziny, piperaziny and the like), aralkyl group having 7 to 13 carbon atoms, amino group optionally mono or di-substituted by alkyl having 1 to 4 carbon atom(s) or  
35       acyl group having 2 to 8 carbon atoms (e.g., alkanoyl group, alkoxy carbonyl group and the like),

alkylsulfonylamino group having 1 to 8 carbon atom(s),  
amidino group, acyl group having 2 to 8 carbon atoms  
(e.g., alkanoyl group, alkoxycarbonyl group and the  
like), alkylsulfonyl group having 1 to 8 carbon atom(s),  
5 carbamoyl group optionally mono or di-substituted by  
alkyl having 1 to 4 carbon atom(s), sulfamoyl group  
optionally mono or di-substituted by alkyl having 1 to 4  
carbon atom(s), carboxyl group, hydroxy group, alkoxy  
group having 1 to 6 carbon atom(s) optionally  
10 substituted by 1 to 3 halogen atom(s) (e.g., fluorine,  
chlorine, bromine, iodine and the like), alkenyloxy  
group having 2 to 5 carbon atoms optionally substituted  
by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine,  
bromine, iodine and the like), cycloalkyloxy group  
15 having 3 to 7 carbon atoms, aralkyloxy group having 7 to  
13 carbon atoms, aryloxy group having 6 to 14 carbon  
atoms (e.g., phenyloxy, naphthyloxy and the like), thiol  
group, alkylthio group having 1 to 6 carbon atom(s)  
optionally substituted by 1 to 3 halogen atom(s) (e.g.,  
20 fluorine, chlorine, bromine, iodine and the like),  
aralkylthio group having 7 to 13 carbon atoms, arylthio  
group having 6 to 14 carbon atoms (e.g., phenylthio,  
naphthylthio and the like), sulfo group, cyano group,  
azide group, nitro group, nitroso group, halogen atom  
25 (e.g., fluorine, chlorine, bromine, iodine) and the like  
can be used.

The "cycloalkyl group having 3 to 10 carbon atoms"  
of the "optionally substituted cycloalkyl group having 3  
to 10 carbon atoms" is, for example, cyclopropyl,  
30 cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl,  
cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl,  
bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl,  
bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl,  
bicyclo[4.3.1]decyl and the like.

35 The "cycloalkenyl group having 3 to 10 carbon  
atoms" of the "optionally substituted cycloalkenyl group

having 3 to 10 carbon atoms" is, for example, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl, 3-cyclohexen-1-yl and the like.

The "optionally substituted cycloalkadienyl group  
5 having 4 to 10 carbon atoms" of the "optionally substituted cycloalkadienyl group having 4 to 10 carbon atoms" is, for example, 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl, 2,5-cyclohexadien-1-yl and the like.

The "aryl group having 6 to 14 carbon atoms" of the  
10 "optionally substituted aryl group having 6 to 14 carbon atoms" is, for example, phenyl, naphthyl, anthryl, phenanthryl, acenaphthylenyl, biphenyl and the like. Of these, phenyl, 1-naphthyl, 2-naphthyl and the like are preferable.

15 The "heterocyclic group" of the "optionally substituted heterocyclic group" is exemplified by non-aromatic heterocyclic group and aromatic heterocyclic group.

The non-aromatic heterocyclic group is, for example,  
20 5 to 7-membered monocyclic non-aromatic heterocyclic group or fused non-aromatic heterocyclic group, containing 1 to 4 heteroatom(s) selected from an oxygen atom, a sulfur atom and a nitrogen atom as a ring-constituting atom, besides carbon atoms. The non-  
25 aromatic fused heterocycle group is, for example, a group wherein these 5 to 7-membered monocyclic non-aromatic heterocyclic groups and a 6-membered ring containing 1 or 2 nitrogen atom(s), a benzene ring or a  
30 5-membered ring containing one sulfur atom are fused and the like.

Preferable examples of the non-aromatic heterocyclic group include 1-pyrroliziny, piperidino, morpholino, thiomorpholino, 1-piperaziny, hexamethylenimin-1-yl, oxazolidin-3-yl, thiazolidin-3-yl,  
35 imidazolidin-3-yl, 2-oxoimidazolidin-1-yl, 2,4-dioxoimidazolidin-3-yl, 2,4-

dioxothiazolidin-3-yl, 1,3-dioxoisindol-2-yl, 5-oxooxadiazol-3-yl, 5-oxothiadiazol-3-yl and the like.

The aromatic heterocyclic group is, for example, a 5 to 7-membered monocyclic aromatic heterocyclic group or fused aromatic heterocyclic group, containing 1 to 4 heteroatom(s) selected from an oxygen atom, a sulfur atom and a nitrogen atom as a ring-constituting atom, besides carbon atoms. The fused aromatic heterocyclic group is, for example, a group where these 5 to 7-membered monocyclic aromatic heterocyclic groups and a 6-membered ring containing 1 or 2 nitrogen atom(s), a benzene ring or a 5-membered ring containing one sulfur atom are fused and the like.

Preferable examples of the aromatic heterocyclic group include 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, isoxazolyl, isothiazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl, 1,3,4-thiadiazol-2-yl, 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl, tetrazol-4-yl, tetrazol-5-yl, 2-quinolyl, 3-quinolyl, 4-quinolyl, 2-quinazolyl, 4-quinazolyl, 2-quinoxalyl, 2-benzofuryl, 3-benzofuryl, 2-benzothienyl, 3-benzothienyl, 2-benzoxazolyl, 2-benzothiazolyl, benzimidazol-1-yl, benzimidazol-2-yl, indol-1-yl, indol-3-yl, 1H-indazol-3-yl, 1H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyridin-6-yl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, 1H-imidazo[4,5-b]pyrazin-2-yl and the like.

The substituent of the aforementioned "optionally substituted cycloalkyl group having 3 to 10 carbon

atoms", "optionally substituted cycloalkenyl group having 3 to 10 carbon atoms", "optionally substituted cycloalkadienyl group having 4 to 10 carbon atoms", "optionally substituted aryl group having 6 to 14 carbon atoms" and "optionally substituted heterocyclic group" is, for example, alkyl group having 1 to 6 carbon atom(s) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine and the like); alkenyl group having 2 to 6 carbon atoms optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine and the like); cycloalkyl group having 3 to 10 carbon atoms; aryl group having 6 to 14 carbon atoms (e.g., phenyl, naphthyl and the like); aromatic heterocyclic group (e.g., thienyl, furyl, pyridyl, oxazolyl, thiazolyl and the like); non-aromatic heterocyclic group (e.g., tetrahydrofuryl, morpholino, thiomorpholino, piperidino, pyrroliziny, piperaziny and the like); aralkyl group having 7 to 13 carbon atoms; amino group optionally mono or di-substituted by alkyl group having 1 to 4 carbon atom(s) or acyl group having 1 to 15 carbon atom(s) (preferably having 2 to 8 carbon atoms) (e.g., alkanoyl group and the like), such as amino, mono- or di-C<sub>2-10</sub> alkanoylamino, C<sub>1-10</sub> alkoxy-carbonylamino, carbamoylamino, mono- or di-C<sub>1-10</sub> alkyl-carbamoylamino, C<sub>6-14</sub> aryl-carbonylamino, C<sub>3-10</sub> cycloalkyl-carbonylamino, C<sub>7-13</sub> aralkyloxy-carbonylamino, mono- or di-C<sub>1-10</sub> alkylsulfonylamino, C<sub>6-14</sub> arylsulfonylamino, C<sub>1-6</sub> alkoxy-carbamoylamino and the like; amidino group; acyl group having 2 to 8 carbon atoms (e.g., alkanoyl group and the like); carbamoyl group optionally mono or di-substituted by alkyl group having 1 to 4 carbon atom(s); sulfamoyl group optionally mono or di-substituted by alkyl group having 1 to 4 carbon atom(s); carboxyl group; alkoxy-carbonyl group having 2 to 8 carbon atoms; hydroxy group; alkoxy group having 1 to 6 carbon atom(s) optionally substituted by 1

to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine and the like); alkenyloxy group having 2 to 5 carbon atoms optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine and the like); cycloalkyloxy group having 3 to 7 carbon atoms; aralkyloxy group having 7 to 13 carbon atoms; aryloxy group having 6 to 14 carbon atoms (e.g., phenyloxy, naphthyloxy and the like); thiol group; alkylthio group having 1 to 6 carbon atom(s) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine and the like); aralkylthio group having 7 to 13 carbon atoms; arylthio group having 6 to 14 carbon atoms (e.g., phenylthio, naphthylthio and the like); sulfo group; cyano group; azide group; nitro group; nitroso group; halogen atom (e.g., fluorine, chlorine, bromine, iodine and the like) and the like. The number of the substituent is, for example, 1 to 3.

The "acyl group" is, for example, a group of the formula:  $-\text{COR}^4$ ,  $-\text{CO}-\text{OR}^4$ ,  $-\text{SO}_2\text{R}^4$ ,  $-\text{SOR}^4$ ,  $-\text{PO}_3\text{R}^4\text{R}^5$ ,  $-\text{CO}-\text{NR}^{4a}\text{R}^{5a}$ ,  $-\text{CS}-\text{NR}^{4a}\text{R}^{5a}$  wherein  $\text{R}^4$  and  $\text{R}^5$  are the same or different and each is hydrogen atom, optionally substituted hydrocarbon group or optionally substituted heterocyclic group.  $\text{R}^{4a}$  and  $\text{R}^{5a}$  are the same or different and each is hydrogen atom, optionally substituted hydrocarbon group or optionally substituted heterocyclic group and  $\text{R}^{4a}$  and  $\text{R}^{5a}$  may form, together with the adjacent nitrogen atom, an optionally substituted, nitrogen-containing heterocycle, and the like.

The "optionally substituted hydrocarbon group" for  $\text{R}^4$ ,  $\text{R}^5$ ,  $\text{R}^{4a}$  and  $\text{R}^{5a}$  is exemplified by "optionally substituted alkyl group having 1 to 10 carbon atom(s)", "optionally substituted alkenyl group having 2 to 10 carbon atoms", "optionally substituted alkynyl group having 2 to 10 carbon atoms", "optionally substituted cycloalkyl group having 3 to 10 carbon atoms", "optionally substituted cycloalkenyl group having 3 to



10 carbon atoms", "optionally substituted cycloalkadienyl group having 4 to 10 carbon atoms", "optionally substituted aryl group having 6 to 14 carbon atoms", "optionally substituted aralkyl group having 7 to 13 carbon atoms", "optionally substituted arylalkenyl group having 8 to 13 carbon atoms" and the like, which are mentioned as the substituents in ring A.

The "aralkyl group having 7 to 13 carbon atoms" of the "optionally substituted aralkyl group having 7 to 13 carbon atoms" is, for example, benzyl, phenethyl, naphthylmethyl and the like.

The "arylalkenyl group having 8 to 13 carbon atoms" of the "optionally substituted arylalkenyl group having 8 to 13 carbon atoms" is, for example, styryl and the like.

The substituent of the "optionally substituted aralkyl group having 7 to 13 carbon atoms" and "optionally substituted arylalkenyl group having 8 to 13 carbon atoms" is exemplified by that mentioned as the substituent in the aforementioned "optionally substituted cycloalkyl group having 3 to 10 carbon atoms" and the like. The number of the substituent is, for example, 1 to 3.

The "optionally substituted heterocyclic group" for  $R^4$ ,  $R^5$ ,  $R^{4a}$  or  $R^{5a}$  is exemplified by that mentioned as the substituent in ring A.

The "nitrogen-containing heterocycle" of the "optionally substituted, nitrogen-containing heterocycle" formed by  $R^{4a}$  and  $R^{5a}$  together with the adjacent nitrogen atom is, for example, a 5 to 7-membered, nitrogen-containing heterocycle containing at least one nitrogen atom and further 1 or 2 heteroatom(s) selected from oxygen atom, sulfur atom and nitrogen atom as a ring-constituting atom, besides carbon atoms. Preferable examples of the nitrogen-containing heterocycle include pyrrolidine, imidazolidine,

pyrazolidine, piperidine, piperazine, morpholine, thiomorpholine and the like.

The nitrogen-containing heterocycle optionally has 1 or 2 substituent(s) at substitutable position(s).

- 5 Examples of the substituent include hydroxy group, C<sub>1-6</sub> alkyl group optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine and the like), C<sub>7-13</sub> aralkyl group (e.g., benzyl, diphenylmethyl and the like) and the like.
- 10 Preferable examples of the "acyl group" include formyl, carboxyl, carbamoyl, C<sub>1-6</sub> alkyl-carbonyl (e.g., acetyl, isobutanoyl, isopentanoyl and the like), C<sub>1-6</sub> alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl and the like), C<sub>6-14</sub> aryl-carbonyl (e.g., benzoyl, 1-naphthoyl, 2-naphthoyl and the like), C<sub>6-14</sub> aryloxy-carbonyl (e.g., phenyloxycarbonyl, naphthyloxycarbonyl and the like), C<sub>7-13</sub> aralkyloxy-carbonyl (e.g., benzyloxycarbonyl, phenethyloxycarbonyl and the like), mono- or di- (C<sub>1-6</sub> alkyl optionally having 1 to 3 substituent(s) selected from halogen atom and C<sub>1-6</sub> alkoxy-carbonyl)-carbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, propylcarbamoyl, trifluoroethylcarbamoyl and the like), C<sub>6-14</sub> aryl-carbamoyl (e.g., phenylcarbamoyl and the like), C<sub>3-10</sub> cycloalkyl-carbamoyl (e.g., cyclopropylcarbamoyl and the like), C<sub>7-13</sub> aralkyl-carbamoyl (e.g., benzylcarbamoyl and the like), C<sub>1-6</sub> alkylsulfonyl (e.g., methylsulfonyl and the like), C<sub>6-14</sub> arylsulfonyl (e.g., phenylsulfonyl and the like), nitrogen-containing heterocycle-carbonyl optionally substituted by hydroxy (e.g., pyrrolidinylcarbonyl, piperidinocarbonyl and the like), C<sub>1-6</sub> alkylsulfinyl (e.g., methylsulfinyl and the like), C<sub>1-6</sub> alkoxy-carbamoyl (e.g., methoxycarbamoyl), aminocarbamoyl, hydroxycarbamoyl, thiocarbamoyl and the
- 35

like.

The "optionally substituted amino group" is, for example, amino group optionally substituted by 1 or 2 substituent(s) selected from alkyl group having 1 to 10 carbon atom(s), alkenyl group having 2 to 10 carbon atoms, cycloalkyl group having 3 to 10 carbon atoms, cycloalkenyl group having 3 to 10 carbon atoms, aryl group having 6 to 14 carbon atoms and acyl.

The "alkyl group having 1 to 10 carbon atom(s)", "alkenyl group having 2 to 10 carbon atoms", "cycloalkyl group having 3 to 10 carbon atoms", "cycloalkenyl group having 3 to 10 carbon atoms", "aryl group having 6 to 14 carbon atoms" and "acyl group" are exemplified by those mentioned as the substituent in ring A.

Preferable examples of the substituted amino group include mono- or di-C<sub>1-10</sub> alkylamino (e.g., methylamino, dimethylamino, ethylamino, diethylamino, propylamino, dibutylamino), mono- or di-C<sub>2-10</sub> alkenylamino (e.g., diallylamino), mono- or di-C<sub>3-10</sub> cycloalkylamino (e.g., cyclohexylamino), mono- or di-C<sub>2-10</sub> alkanoylamino (e.g., acetylamino, propionylamino, butanoylamino, isobutanoylamino, isopentanoylamino), C<sub>6-14</sub> aryl-carbonylamino (e.g., benzoylamino), C<sub>6-14</sub> arylamino (e.g., phenylamino), carbamoylamino, mono- or di-C<sub>1-10</sub> alkyl-carbamoylamino (e.g., methylcarbamoylamino, dimethylcarbamoylamino), C<sub>1-10</sub> alkoxy-carbonylamino (e.g., methoxycarbonylamino), C<sub>7-13</sub> aralkyloxy-carbonylamino (e.g., benzyloxycarbonylamino), C<sub>3-10</sub> cycloalkyl-carbonylamino (e.g., cyclopentylcarbonylamino, cyclohexylcarbonylamino), mono- or di-C<sub>1-10</sub> alkylsulfonylamino (e.g., methylsulfonylamino, dimethylsulfonylamino), C<sub>6-14</sub> arylsulfonylamino (e.g., phenylsulfonylamino), C<sub>1-6</sub> alkoxy-carbamoylamino (e.g., methoxycarbamoylamino) and the like.

The "optionally substituted hydroxy group" is, for example, hydroxy group optionally substituted by "alkyl

group having 1 to 10 carbon atom(s)", "alkenyl group having 2 to 10 carbon atoms", "alkynyl group having 2 to 10 carbon atoms", "cycloalkyl group having 3 to 10 carbon atoms", "cycloalkenyl group having 3 to 10 carbon atoms", "aryl group having 6 to 14 carbon atoms" or "aralkyl group having 7 to 13 carbon atoms", each of which is optionally substituted.

The "alkyl having 1 to 10 carbon atom(s)", "alkenyl group having 2 to 10 carbon atoms", "alkynyl group having 2 to 10 carbon atoms", "cycloalkyl group having 3 to 10 carbon atoms", "cycloalkenyl group having 3 to 10 carbon atoms", "aryl group having 6 to 14 carbon atoms" and "aralkyl having 7 to 13 carbon atoms" are exemplified by those mentioned as the aforementioned R<sup>4</sup> and the like.

These "alkyl group having 1 to 10 carbon atom(s)", "alkenyl group having 2 to 10 carbon atoms", "alkynyl group having 2 to 10 carbon atoms", "cycloalkyl group having 3 to 10 carbon atoms", "cycloalkenyl group having 3 to 10 carbon atoms", "aryl group having 6 to 14 carbon atoms" and "aralkyl group having 7 to 13 carbon atoms" each optionally have 1 to 3 substituent(s) at substitutable position(s). Such substituents are, for example, halogen atom (e.g., fluorine, chlorine, bromine, iodine and the like), alkoxy group having 1 to 3 carbon atom(s), alkoxycarbonyl group having 2 to 5 carbon atoms, alkanoyl group having 2 to 5 carbon atoms, cyano group, carbamoyl group, hydroxy group, cycloalkyl group having 3 to 10 carbon atoms, carboxyl group, amino group, alkanoylamino group having 2 to 5 carbon atoms and the like.

The substituted hydroxy group is preferably "alkoxy group having 1 to 10 carbon atom(s)", "alkenyloxy group having 2 to 10 carbon atoms", "alkynyloxy group having 2 to 10 carbon atoms", "cycloalkyloxy group having 3 to 10 carbon atoms", "cycloalkenyloxy group having 3 to 10

carbon atoms", "aryloxy group having 6 to 14 carbon atoms", "aralkyloxy group having 7 to 13 carbon atoms" and the like, each optionally having 1 to 3 substituent(s) selected from halogen atom (e.g.,  
5 fluorine, chlorine, bromine, iodine and the like), alkoxy group having 1 to 3 carbon atom(s), alkoxycarbonyl group having 2 to 5 carbon atoms, alkanoyl group having 2 to 5 carbon atoms, cyano group, carbamoyl group, hydroxy group, carboxyl group, amino  
10 group, alkanoylamino group having 2 to 5 carbon atoms and cycloalkyl group having 3 to 10 carbon atoms.

The "alkoxy group having 1 to 10 carbon atom(s)" is, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec.-butoxy, t.-butoxy, pentyloxy,  
15 isopentyloxy, neopentyloxy, hexyloxy, heptyloxy, nonyloxy and the like.

The "alkenyloxy group having 2 to 10 carbon atoms" is, for example, allyloxy, crotyloxy, 2-pentenylloxy, 3-hexenyloxy and the like.

20 The "alkynyloxy group having 2 to 10 carbon atoms" is, for example, ethynyloxy, propynyloxy, pentynyloxy and the like.

The "cycloalkyloxy group having 3 to 10 carbon atoms" is, for example, cyclobutoxy, cyclopentyloxy,  
25 cyclohexyloxy and the like.

The "cycloalkenyloxy group having 3 to 10 carbon atoms" is, for example, 2-cyclopentenylloxy, 2-cyclohexenyloxy and the like.

The "aryloxy group having 6 to 14 carbon atoms" is,  
30 for example, phenoxy, naphthyloxy and the like.

The "aralkyloxy group having 7 to 13 carbon atoms" is, for example, benzyloxy, phenethyloxy, naphthylmethyloxy and the like.

The substituted hydroxy group is more preferably  
35 "alkoxy group having 1 to 10 carbon atom(s)", "cycloalkyloxy group having 3 to 10 carbon atoms" or

"aralkyloxy group having 7 to 13 carbon atoms", each optionally having 1 to 3 substituent(s) selected from halogen atom (e.g., fluorine, chlorine, bromine, iodine and the like), alkoxy group having 1 to 3 carbon atom(s),  
5 alkoxy carbonyl group having 2 to 5 carbon atoms, alkanoyl group having 2 to 5 carbon atoms, cyano group, carbamoyl group, hydroxy group, carboxyl group, amino group, alkanoylamino group having 2 to 5 carbon atoms and cycloalkyl group having 3 to 10 carbon atoms.

10 The "optionally substituted thiol group" is, for example, thiol group optionally substituted by "alkyl group having 1 to 10 carbon atom(s)", "alkenyl group having 2 to 10 carbon atoms", "alkynyl group having 2 to 10 carbon atoms", "cycloalkyl group having 3 to 10  
15 carbon atoms", "cycloalkenyl group having 3 to 10 carbon atoms", "aryl group having 6 to 14 carbon atoms" or "aralkyl group having 7 to 13 carbon atoms", each of which is optionally substituted.

These "alkyl group having 1 to 10 carbon atom(s)",  
20 "alkenyl group having 2 to 10 carbon atoms", "alkynyl group having 2 to 10 carbon atoms", "cycloalkyl group having 3 to 10 carbon atoms", "cycloalkenyl group having 3 to 10 carbon atoms", "aryl group having 6 to 14 carbon atoms" and "aralkyl group having 7 to 13 carbon atoms"  
25 are exemplified by those mentioned as the aforementioned R<sup>4</sup> and the like.

These "alkyl group having 1 to 10 carbon atom(s)", "alkenyl group having 2 to 10 carbon atoms", "alkynyl group having 2 to 10 carbon atoms", "cycloalkyl group  
30 having 3 to 10 carbon atoms", "cycloalkenyl group having 3 to 10 carbon atoms", "aryl group having 6 to 14 carbon atoms" and "aralkyl group having 7 to 13 carbon atoms" each optionally have 1 to 3 substituent(s) at substitutable position(s). These substituents are, for  
35 example, halogen atom (e.g., fluorine, chlorine, bromine, iodine and the like), alkoxy group having 1 to 3 carbon

atom(s), alkoxycarbonyl group having 2 to 5 carbon atoms, alkanoyl group having 2 to 5 carbon atoms, cyano group, carbamoyl group, hydroxy group, cycloalkyl group having 3 to 10 carbon atoms, carboxyl group, amino group, 5 alkanoylamino group having 2 to 5 carbon atoms and the like.

The substituted thiol group is preferably "alkylthio group having 1 to 10 carbon atom(s)", "alkenylthio group having 2 to 10 carbon atoms", 10 "alkynylthio group having 2 to 10 carbon atoms", "cycloalkylthio group having 3 to 10 carbon atoms", "cycloalkenylthio group having 3 to 10 carbon atoms", "arylthio group having 6 to 14 carbon atoms", "aralkylthio group having 7 to 13 carbon atoms" and the 15 like, each optionally having 1 to 3 substituent(s) selected from halogen atom (e.g., fluorine, chlorine, bromine, iodine and the like), alkoxy group having 1 to 3 carbon atom(s), alkoxycarbonyl group having 2 to 5 carbon atoms, alkanoyl group having 2 to 5 carbon atoms, 20 cyano group, carbamoyl group, hydroxy group, carboxyl group, amino group, alkanoylamino group having 2 to 5 carbon atoms and cycloalkyl group having 3 to 10 carbon atoms.

The "alkylthio group having 1 to 10 carbon atom(s)" 25 is, for example, methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec.-butylthio, t.-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio, heptylthio, nonylthio and the like.

The "alkenylthio group having 2 to 10 carbon atoms" 30 is, for example, allylthio, crotylthio, 2-pentenylthio, 3-hexenylthio and the like.

The "alkynylthio group having 2 to 10 carbon atoms" is, for example, ethynylthio, propynylthio, pentynylthio and the like.

35 The "cycloalkylthio group having 3 to 10 carbon atoms" is, for example, cyclobutylthio, cyclopentylthio,

cyclohexylthio and the like.

The "cycloalkenylthio group having 3 to 10 carbon atoms" is, for example, 2-cyclopentenylthio, 2-cyclohexenylthio and the like.

5       The "arylthio group having 6 to 14 carbon atoms" is, for example, phenylthio, naphthylthio and the like.

The "aralkylthio having 7 to 13 carbon atoms" is, for example, benzylthio, phenethylthio, naphthylmethylthio and the like.

10       The substituted thiol group is more preferably alkylthio group having 1 to 10 carbon atom(s) optionally substituted by carbamoyl group.

Preferable examples of the "substituent" of "5 to 10-membered aromatic ring" for ring A are

- 15 1) a halogen atom (e.g., fluorine, chlorine, bromine, iodine and the like);  
2) a nitro group;  
3) a cyano group;  
4) a C<sub>1-3</sub> alkylenedioxy group (e.g., methylenedioxy);  
20 5) a C<sub>1-10</sub> alkyl group (e.g., methyl, ethyl) or a C<sub>2-10</sub> alkenyl group (e.g., ethenyl), each optionally having 1 to 3 substituent(s) selected from halogen atom, hydroxy group, carboxyl group, alkoxycarbonyl group having 2 to 8 carbon atoms (e.g., ethoxycarbonyl), carbamoyl group,  
25 cyano group, amino group, alkanoylamino group having 2 to 8 carbon atoms (e.g., acetylamino, isobutanoylamino), alkoxycarbonylamino group having 2 to 8 carbon atoms (e.g., ethoxycarbonylamino) and alkylsulfonylamino group having 1 to 8 carbon atom(s) (e.g.,  
30 methylsulfonylamino);  
6) an optionally substituted hydroxy group [e.g., alkoxy group having 1 to 10 carbon atom(s) (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy), cycloalkyloxy group having 3 to 10 carbon atoms (e.g.,  
35 cyclopentyloxy) or aralkyloxy group having 7 to 13 carbon atoms (e.g., benzyloxy), each optionally having 1



- to 3 substituent(s) selected from halogen atom, alkoxy group having 1 to 3 carbon atom(s) (e.g., methoxy), alkoxy-carbonyl group having 2 to 5 carbon atoms (e.g., methoxycarbonyl, ethoxycarbonyl), alkanoyl group having 2 to 5 carbon atoms (e.g., pivaloyl), cyano group, carbamoyl group, hydroxy group, carboxyl group, amino group, alkanoylamino group having 2 to 5 carbon atoms (e.g., acetylamino) and cycloalkyl group having 3 to 10 carbon atoms (e.g., cyclopropyl, cyclohexyl); hydroxy group];
- 7) an acyl group [e.g., formyl, carboxyl, C<sub>1-6</sub> alkyl-carbonyl (e.g., acetyl), C<sub>1-6</sub> alkoxy-carbonyl (e.g., methoxycarbonyl), carbamoyl, aminocarbamoyl, hydroxycarbamoyl, mono- or di-(C<sub>1-6</sub> alkyl optionally having 1 to 3 substituent(s) selected from halogen atom and C<sub>1-6</sub> alkoxy-carbonyl (e.g., ethoxycarbonyl))-carbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, dimethylcarbamoyl, trifluoroethylcarbamoyl, ethoxycarbonylmethylcarbamoyl and the like), C<sub>3-10</sub> cycloalkyl-carbamoyl (e.g., cyclopropylcarbamoyl), C<sub>7-13</sub> aralkyl-carbamoyl (e.g., benzylcarbamoyl), nitrogen-containing heterocycle-carbonyl optionally substituted by hydroxy (e.g., pyrrolidinylcarbonyl, piperidinocarbonyl), C<sub>1-6</sub> alkylsulfonyl (e.g., methylsulfonyl), C<sub>1-6</sub> alkylsulfinyl (e.g., methylsulfinyl), thiocarbamoyl];
- 8) an optionally substituted amino group [e.g., amino, mono- or di-C<sub>2-10</sub> alkanoylamino (e.g., acetylamino, propionylamino, isobutanoylamino, isopentanoylamino), C<sub>1-10</sub> alkoxy-carbonylamino (e.g., methoxycarbonylamino), carbamoylamino, mono- or di-C<sub>1-10</sub> alkyl-carbamoylamino (e.g., methylcarbamoylamino, dimethylcarbamoylamino), C<sub>6-14</sub> aryl-carbonylamino (e.g., benzoylamino), C<sub>3-10</sub> cycloalkyl-carbonylamino (e.g., cyclopentylcarbonylamino), C<sub>7-13</sub> aralkyloxy-carbonylamino (e.g., benzyloxycarbonylamino), mono- or di-C<sub>1-10</sub>

- alkylsulfonylamino (e.g., methylsulfonylamino, dimethylsulfonylamino), C<sub>6-14</sub> arylsulfonylamino (e.g., phenylsulfonylamino), C<sub>1-6</sub> alkoxy-carbamoylamino (e.g., methoxycarbamoylamino)];
- 5 9) an aryl group having 6 to 14 carbon atoms (e.g., phenyl);
- 10) an optionally substituted thiol group [e.g., alkylthio group having 1 to 10 carbon atom(s) optionally substituted by carbamoyl group (e.g., methylthio)];
- 10 11) an optionally substituted heterocyclic group [e.g., aromatic heterocyclic group (preferably furyl, thienyl, oxazolyl, oxadiazolyl, thiazolyl, tetrazolyl, pyridyl, pyrrolyl, triazolyl) or non-aromatic heterocyclic group (preferably dioxoisindole, 5-oxooxadiazol-3-yl, 5-
- 15 oxothiadiazol-3-yl), each optionally having 1 or 2 substituent(s) selected from C<sub>1-6</sub> alkyl group optionally substituted by 1 to 3 halogen atom(s) (e.g., methyl, trifluoromethyl), carboxyl group, alkoxy-carbonyl group having 2 to 8 carbon atoms (preferably ethoxycarbonyl),
- 20 cyano group, carbamoyl group, amino group, mono- or di-C<sub>2-10</sub> alkanoylamino group (e.g., acetylamino, isopentanoylamino), C<sub>1-10</sub> alkoxy-carbonylamino group (e.g., methoxycarbonylamino), carbamoylamino group, mono- or di-C<sub>1-10</sub> alkyl-carbamoylamino group (e.g.,
- 25 methylcarbamoylamino, dimethylcarbamoylamino), C<sub>6-14</sub> aryl-carbonylamino group (e.g., benzoylamino), C<sub>3-10</sub> cycloalkyl-carbonylamino group, C<sub>7-13</sub> aralkyloxy-carbonylamino group, mono- or di-C<sub>1-10</sub> alkylsulfonylamino group (e.g., methylsulfonylamino, dimethylsulfonylamino),
- 30 C<sub>6-14</sub> arylsulfonylamino group and C<sub>1-6</sub> alkoxy-carbamoylamino group (e.g., methoxycarbamoylamino)];
- 12) an amidino group; and the like.

The number of substituent is preferably 1 to 3,  
35 more preferably 1 or 2.

The "substituent" of the "5 to 10-membered aromatic

ring" for ring A is preferably

- 1) a halogen atom (e.g., fluorine, chlorine, bromine, iodine and the like);
- 2) a nitro group;
- 5 3) a cyano group;
- 4) a C<sub>1-3</sub> alkylenedioxy group (e.g., methylenedioxy);
- 5) a C<sub>1-10</sub> alkyl group or a C<sub>2-10</sub> alkenyl group, each optionally having 1 to 3 substituent(s) selected from halogen atom, hydroxy group, carboxyl group,
- 10 alkoxy-carbonyl group having 2 to 8 carbon atoms, carbamoyl group, cyano group, amino group, alkanoylamino group having 2 to 8 carbon atoms, alkoxy-carbonylamino group having 2 to 8 carbon atoms, alkylsulfonylamino group having 1 to 8 carbon atoms;
- 15 6) an optionally substituted hydroxy group (e.g., alkoxy group having 1 to 10 carbon atom(s), cycloalkyloxy group having 3 to 10 carbon atoms or aralkyloxy group having 7 to 13 carbon atoms, each optionally having 1 to 3 substituent(s) selected from halogen atom, alkoxy group
- 20 having 1 to 3 carbon atom(s), alkoxy-carbonyl group having 2 to 5 carbon atoms, alkanoyl group having 2 to 5 carbon atoms, cyano group, carbamoyl group, hydroxy group, carboxyl group and cycloalkyl group having 3 to 10 carbon atoms; hydroxy group);
- 25 7) an acyl group (e.g., carboxyl, C<sub>1-6</sub> alkoxy-carbonyl, carbamoyl, mono- or di-(C<sub>1-6</sub> alkyl optionally having 1 to 3 substituent(s) selected from halogen atom and C<sub>1-6</sub> alkoxy-carbonyl)-carbamoyl, C<sub>3-10</sub> cycloalkyl-carbamoyl, C<sub>7-13</sub> aralkyl-carbamoyl, nitrogen-containing heterocycle-
- 30 carbonyl optionally substituted by hydroxy, C<sub>1-6</sub> alkyl-carbonyl, thiocarbamoyl, C<sub>1-6</sub> alkylsulfonyl, C<sub>1-6</sub> alkylsulfinyl);
- 8) an optionally substituted amino group (e.g., amino, mono- or di-C<sub>2-10</sub> alkanoylamino, C<sub>1-10</sub> alkoxy-carbonylamino,
- 35 mono- or di-C<sub>1-10</sub> alkyl-carbamoylamino, C<sub>6-14</sub> aryl-carbonylamino, C<sub>3-10</sub> cycloalkyl-carbonylamino, C<sub>7-13</sub>

aralkyloxy-carbonylamino, mono- or di-C<sub>1-10</sub>  
alkylsulfonylamino, C<sub>6-14</sub> arylsulfonylamino,  
carbamoylamino); or

- 9) an optionally substituted heterocyclic group [e.g.,  
5 aromatic heterocyclic group (preferably furyl, thienyl,  
oxazolyl, oxadiazolyl, thiazolyl, tetrazolyl, pyridyl,  
pyrrolyl, triazolyl) or non-aromatic heterocyclic group  
(preferably dioxoisindole, 5-oxooxadiazol-3-yl, 5-  
oxothiadiazol-3-yl)], each optionally having 1 or 2  
10 substituent(s) selected from C<sub>1-6</sub> alkyl group optionally  
substituted by 1 to 3 halogen atom(s), carboxyl group,  
alkoxycarbonyl group having 2 to 8 carbon atoms, cyano  
group, carbamoyl group, amino group, mono- or di-C<sub>2-10</sub>  
alkanoylamino group, C<sub>1-10</sub> alkoxy-carbonylamino group,  
15 carbamoylamino group, mono- or di-C<sub>1-10</sub> alkyl-  
carbamoylamino group, C<sub>6-14</sub> aryl-carbonylamino group, C<sub>3-10</sub>  
cycloalkyl-carbonylamino group, C<sub>7-13</sub> aralkyloxy-  
carbonylamino group, mono- or di-C<sub>1-10</sub> alkylsulfonylamino  
group, C<sub>6-14</sub> arylsulfonylamino group and C<sub>1-6</sub> alkoxy-  
20 carbamoylamino group.

The number of substituent is preferably 1 to 3,  
more preferably 1 or 2.

The "substituent" of the "5 to 10-membered aromatic  
ring" for ring A is more preferably

- 25 1) a halogen atom (e.g., fluorine, chlorine, bromine,  
iodine and the like);  
2) a nitro group;  
3) a cyano group;  
4) a C<sub>1-3</sub> alkylenedioxy group (e.g., methylenedioxy);  
30 5) an optionally substituted hydroxy group (preferably  
methoxy, carbamoylmethoxy and the like);  
6) an acyl group (preferably carbamoyl, methoxycarbonyl  
and the like);  
7) an optionally substituted amino group (preferably  
35 acetylamino and the like);  
8) a C<sub>1-10</sub> alkyl group (preferably ethyl) or a C<sub>2-10</sub>

alkenyl group (preferably ethenyl), each optionally substituted by carbamoyl group;

- 9) an optionally substituted heterocyclic group [e.g., aromatic heterocyclic group (preferably furyl, thienyl, oxazolyl, oxadiazolyl, thiazolyl, tetrazolyl, pyridyl, pyrrolyl, triazolyl) or non-aromatic heterocyclic group (preferably dioxoisindole, 5-oxooxadiazol-3-yl, 5-oxothiadiazol-3-yl), each optionally having 1 or 2 substituent(s) selected from C<sub>1-6</sub> alkyl group optionally substituted by 1 to 3 halogen atom(s), carboxyl group, alkoxy-carbonyl group having 2 to 8 carbon atoms, cyano group, carbamoyl group, amino group, mono- or di-C<sub>2-10</sub> alkanoylamino group, C<sub>1-10</sub> alkoxy-carbonylamino group, carbamoylamino group, mono- or di-C<sub>1-10</sub> alkyl-carbamoylamino group, C<sub>6-14</sub> aryl-carbonylamino group, C<sub>3-10</sub> cycloalkyl-carbonylamino group, C<sub>7-13</sub> aralkyloxy-carbonylamino group, mono- or di-C<sub>1-10</sub> alkylsulfonylamino group, C<sub>6-14</sub> arylsulfonylamino group and C<sub>1-6</sub> alkoxy-carbamoylamino group]. The number of substituent is preferably 1 or 2.

The ring A is preferably benzene ring optionally having 1 or 2 substituent(s) selected from

- 1) a cyano group;
- 2) a C<sub>1-10</sub> alkyl group (preferably ethyl) or a C<sub>2-10</sub> alkenyl group (preferably ethenyl), each optionally having 1 to 3 substituent(s) selected from carbamoyl group, carboxyl group and alkoxy-carbonyl group having 2 to 8 carbon atoms (preferably methoxycarbonyl);
- 3) an optionally substituted hydroxy group [preferably alkoxy group having 1 to 10 carbon atom(s) (preferably methoxy, isopropoxy) optionally having 1 to 3 substituent(s) selected from carbamoyl group, carboxyl group and alkoxy-carbonyl group having 2 to 5 carbon atoms (preferably methoxycarbonyl); hydroxy group; aralkyloxy group having 7 to 13 carbon atoms (preferably benzyloxy)] [more preferably carbamoylmethoxy];

- 4) an acyl group [preferably C<sub>1-6</sub> alkyl-carbonyl (preferably acetyl), carbamoyl, mono- or di- (C<sub>1-6</sub> alkyl optionally having 1 to 3 substituent(s) selected from halogen atom and C<sub>1-6</sub> alkoxy-carbonyl)-carbamoyl
- 5 (preferably methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, dimethylcarbamoyl, trifluoroethylcarbamoyl, ethoxycarbonylmethylcarbamoyl and the like), C<sub>3-10</sub> cycloalkyl-carbamoyl (preferably cyclopropylcarbamoyl), C<sub>7-13</sub> aralkyl-carbamoyl
- 10 (preferably benzylcarbamoyl), nitrogen-containing heterocycle-carbonyl optionally substituted by hydroxy (preferably pyrrolidinylcarbonyl, piperidinocarbonyl), C<sub>1-6</sub> alkylsulfonyl (preferably methylsulfonyl), C<sub>1-6</sub> alkylsulfinyl (preferably methylsulfinyl), carboxyl, C<sub>1-6</sub>
- 15 alkoxy-carbonyl (preferably methoxycarbonyl), thiocarbamoyl];
- 5) an optionally substituted amino group (preferably carbamoylamino);
- 6) an optionally substituted thiol group [preferably
- 20 alkylthio group having 1 to 10 carbon atom(s) optionally substituted by carbamoyl group (preferably methylthio)];
- 7) an optionally substituted heterocyclic group [preferably aromatic heterocyclic group (preferably furyl, thienyl, oxazolyl, oxadiazolyl, thiazolyl,
- 25 tetrazolyl, pyridyl, pyrrolyl, triazolyl) or non-aromatic heterocyclic group (preferably dioxoisindole, 5-oxooxadiazol-3-yl, 5-oxothiadiazol-3-yl), each optionally having 1 or 2 substituent(s) selected from C<sub>1-6</sub>
- 6 alkyl group optionally substituted by 1 to 3 halogen
- 30 atom(s) (preferably methyl, trifluoromethyl), carboxyl group, alkoxycarbonyl group having 2 to 8 carbon atoms (preferably ethoxycarbonyl), cyano group, carbamoyl group, amino group, mono- or di-C<sub>2-10</sub> alkanoylamino group (e.g., acetylamino, isopentanoylamino), C<sub>1-10</sub> alkoxy-
- 35 carbonylamino group (e.g., methoxycarbonylamino), carbamoylamino group, mono- or di-C<sub>1-10</sub> alkyl-

carbamoylamino group (e.g., methylcarbamoylamino, dimethylcarbamoylamino), C<sub>6-14</sub> aryl-carbonylamino group (e.g., benzoylamino), C<sub>3-10</sub> cycloalkyl-carbonylamino group, C<sub>7-13</sub> aralkyloxy-carbonylamino group, mono- or di-  
5 C<sub>1-10</sub> alkylsulfonylamino group (e.g., methylsulfonylamino, dimethylsulfonylamino), C<sub>6-14</sub> arylsulfonylamino group and C<sub>1-6</sub> alkoxy-carbamoylamino group (e.g., methoxycarbamoylamino)]; and  
8) an amidino group.

10 The ring A is more preferably a benzene ring having 1 or 2 substituent(s) selected from

1) a C<sub>1-10</sub> alkyl group (preferably ethyl) or a C<sub>2-10</sub> alkenyl group (preferably ethenyl), each having 1 to 3 substituent(s) selected from carbamoyl group, carboxyl  
15 group and alkoxycarbonyl group having 2 to 8 carbon atoms (preferably methoxycarbonyl);

2) an optionally substituted hydroxy group [preferably alkoxy group having 1 to 10 carbon atom(s) (preferably methoxy, isopropoxy) optionally having 1 to 3

20 substituent(s) selected from carbamoyl group, carboxyl group and alkoxycarbonyl group having 2 to 5 carbon

atoms (preferably methoxycarbonyl) ; hydroxy group; aralkyloxy group having 7 to 13 carbon atom(s). (preferably benzyloxy)] [more preferably

25 carbamoylmethoxy];

3) an acyl group [preferably C<sub>1-6</sub> alkyl-carbonyl (preferably acetyl), carbamoyl, mono- or di- (C<sub>1-6</sub> alkyl optionally having 1 to 3 substituent(s) selected from halogen atom and C<sub>1-6</sub> alkoxy-carbonyl)-carbamoyl

30 (preferably methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, dimethylcarbamoyl, trifluoroethylcarbamoyl, ethoxycarbonylmethylcarbamoyl and the like), C<sub>3-10</sub> cycloalkyl-carbamoyl (preferably cyclopropylcarbamoyl), C<sub>7-13</sub> aralkyl-carbamoyl

35 (preferably benzylcarbamoyl), nitrogen-containing heterocycle-carbonyl optionally substituted by hydroxy

- (preferably pyrrolidinylcarbonyl, piperidinocarbonyl),  
 C<sub>1-6</sub> alkylsulfonyl (preferably methylsulfonyl), C<sub>1-6</sub>  
 alkylsulfinyl (preferably methylsulfinyl), carboxyl, C<sub>1-6</sub>  
 alkoxy-carbonyl (preferably methoxycarbonyl),  
 5 thiocarbamoyl]; and  
 4) an optionally substituted heterocyclic group  
 [preferably aromatic heterocyclic group (preferably  
 furyl, thienyl, oxazolyl, oxadiazolyl, thiazolyl,  
 tetrazolyl, pyridyl, pyrrolyl, triazolyl) or non-  
 10 aromatic heterocyclic group (preferably dioxoisindole,  
 5-oxoxadiazol-3-yl, 5-oxothiadiazol-3-yl), each  
 optionally having 1 or 2 substituent(s) selected from C<sub>1-6</sub>  
 alkyl optionally substituted by 1 to 3 halogen atom(s)  
 (preferably methyl, trifluoromethyl), carboxyl group,  
 15 alkoxy-carbonyl group having 2 to 8 carbon atoms  
 (preferably ethoxycarbonyl), cyano group, carbamoyl  
 group, amino, mono- or di-C<sub>2-10</sub> alkanoylamino (e.g.,  
 acetylamino, isopentanoylamino), C<sub>1-10</sub> alkoxy-  
 carbonylamino (e.g., methoxycarbonylamino),  
 20 carbamoylamino, mono- or di-C<sub>1-10</sub> alkyl-carbamoylamino  
 (e.g., methylcarbamoylamino, dimethylcarbamoylamino), C<sub>6-14</sub>  
 aryl-carbonylamino (e.g., benzoylamino), C<sub>3-10</sub>  
 cycloalkyl-carbonylamino, C<sub>7-13</sub> aralkyloxy-carbonylamino,  
 mono- or di-C<sub>1-10</sub> alkylsulfonylamino (e.g.,  
 25 methylsulfonylamino, dimethylsulfonylamino), C<sub>6-14</sub>  
 arylsulfonylamino and C<sub>1-6</sub> alkoxy-carbamoylamino (e.g.,  
 methoxycarbamoylamino)].

Examples of the "optionally substituted hydrocarbon  
 group" for R<sup>1</sup> and R<sup>2</sup> are those exemplified for the  
 30 aforementioned R<sup>4</sup> and the like.

Examples of the "optionally substituted  
 heterocyclic group" for R<sup>1</sup> and R<sup>2</sup> are those exemplified  
 as the substituent in ring A.

R<sup>1</sup> is preferably an optionally substituted  
 35 hydrocarbon and more preferably an alkyl group having 1  
 to 10 carbon atom(s) which is optionally substituted by



cycloalkyl group having 3 to 10 carbon atoms (e.g., cyclopropyl and the like).  $R^1$  is particularly preferably an alkyl group having 4 to 10 carbon atoms or a cycloalkylalkyl group having 4 to 10 carbon atoms (preferably cyclopropylmethyl). Of these, preferred is an alkyl group having 4 or 5 carbon atoms (e.g., butyl, isobutyl, sec.-butyl, t.-butyl, pentyl, isopentyl, neopentyl, 1-ethylpropyl and the like).

$R^2$  is preferably an optionally substituted hydrocarbon group. More preferably,  $R^2$  is an alkyl group having 1 to 10 substituent(s) (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, t.-butyl, pentyl and the like), aryl group having 6 to 14 carbon atoms (e.g., phenyl and the like) or aralkyl group having 7 to 13 carbon atoms (e.g., benzyl, phenethyl, naphthylmethyl and the like), each optionally having 1 to 3 (preferably 1 or 2) substituent(s) selected from halogen atom (e.g., fluorine, chlorine and the like), hydroxy group, nitro group, amino group, optionally halogenated alkyl group having 1 to 6 carbon atom(s) (e.g., trifluoromethyl, methyl and the like), alkoxy group having 1 to 6 carbon atom(s) (e.g., methoxy and the like), aromatic heterocyclic group (e.g., quinolyl, thienyl and the like) and cycloalkyl group having 3 to 10 carbon atoms (e.g., cyclopentyl and the like).

X is a bond, -O-, -S-, -SO-, -SO<sub>2</sub>- or -NR<sup>3</sup>- ( $R^3$  is hydrogen atom or optionally substituted hydrocarbon group).

Examples of the "optionally substituted hydrocarbon group" for  $R^3$  are those exemplified for the aforementioned  $R^4$  and the like. The "optionally substituted hydrocarbon group" is preferably alkyl group having 1 to 10 carbon atom(s) (e.g., methyl, ethyl and the like) and the like.

In the formula (I), when X is a bond,  $R^2$  is preferably an aryl group having 6 to 14 carbon atoms

(e.g., phenyl and the like) optionally having 1 or 2 substituent(s) selected from halogen atom (e.g., fluorine, chlorine and the like), hydroxy group, nitro group, amino group, optionally halogenated alkyl group  
 5 having 1 to 6 carbon atom(s) (e.g., trifluoromethyl, methyl and the like), alkoxy group having 1 to 6 carbon atom(s) (e.g., methoxy and the like), aromatic heterocyclic group (e.g., quinolyl, thienyl and the like) and cycloalkyl group having 3 to 10 carbon atoms  
 10 (e.g., cyclopentyl and the like).

In the formula (I), when X is -O-, -S-, -SO-, -SO<sub>2</sub>- or -NR<sup>3</sup>-, R<sup>2</sup> is preferably an alkyl group having 1 to 10 carbon atom(s) (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, t.-butyl, pentyl and the  
 15 like) or an aralkyl group having 7 to 13 carbon atoms (e.g., benzyl and the like), each optionally having 1 to 3 (preferably 1 or 2) substituent(s) selected from halogen atom (e.g., fluorine and the like), hydroxy group, nitro group, optionally halogenated alkyl group  
 20 having 1 to 6 carbon atom(s) (e.g., trifluoromethyl and the like), alkoxy group having 1 to 6 carbon atom(s) (e.g., methoxy and the like), aromatic heterocyclic group (e.g., quinolyl, thienyl and the like) and cycloalkyl group having 3 to 10 substituents (e.g.,  
 25 cyclopentyl and the like).

X is preferably a bond or -O-.

The "divalent hydrocarbon group" for L is, for example,

- (1) C<sub>1-10</sub> alkylene (e.g., -CH<sub>2</sub>-, -(CH<sub>2</sub>)<sub>2</sub>-, -(CH<sub>2</sub>)<sub>3</sub>-, -  
 30 (CH<sub>2</sub>)<sub>4</sub>-, -(CH<sub>2</sub>)<sub>5</sub>-, -(CH<sub>2</sub>)<sub>6</sub>-, -CHCH<sub>3</sub>-, -C(CH<sub>3</sub>)<sub>2</sub>-, -(CH(CH<sub>3</sub>))<sub>2</sub>-, -(CH<sub>2</sub>)<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>-, -(CH<sub>2</sub>)<sub>3</sub>C(CH<sub>3</sub>)<sub>2</sub>- and the like);
- (2) C<sub>2-10</sub> alkenylene (e.g., -CH=CH-, -CH<sub>2</sub>-CH=CH-, -CH=CH-  
 CH<sub>2</sub>-, -CH=CH-CH<sub>2</sub>-CH<sub>2</sub>-, -C(CH<sub>3</sub>)<sub>2</sub>-CH=CH-, -CH<sub>2</sub>-CH=CH-CH<sub>2</sub>-, -  
 35 CH<sub>2</sub>-CH<sub>2</sub>-CH=CH-, -CH=CH-CH=CH-, -CH=CH-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>- and the like); or

(3) C<sub>2-10</sub> alkynylene (e.g., -C≡C-, -CH<sub>2</sub>-C≡C-, -CH<sub>2</sub>-C≡C-CH<sub>2</sub>-CH<sub>2</sub>- and the like) and the like.

The "divalent hydrocarbon group" is preferably C<sub>1-10</sub> alkylene, more preferably -CH<sub>2</sub>-, -(CH<sub>2</sub>)<sub>2</sub>- and the like.

5 Particularly, -CH<sub>2</sub>- is preferable.

Preferable examples of compound (I) include the following compounds.

[compound A]

A compound wherein ring A is a benzene ring, a  
10 naphthalene ring or a thiophene ring, each optionally having 1 or 2 substituent(s) selected from

- 1) a halogen atom;
- 2) a nitro group;
- 3) a cyano group;
- 15 4) a C<sub>1-3</sub> alkylendioxy group;
- 5) an optionally substituted hydroxy group (preferably methoxy, carbamoylmethoxy and the like);
- 6) an acyl group (preferably carbamoyl, methoxycarbonyl and the like); and
- 20 7) an optionally substituted amino group (preferably acetyl amino and the like);

R<sup>1</sup> is an alkyl group having 1 to 10 carbon atom(s) (preferably alkyl group having 4 to 10 carbon atom(s));

R<sup>2</sup> is an alkyl group having 1 to 10 carbon atom(s), an  
25 aryl group having 6 to 14 carbon atoms or an aralkyl group having 7 to 13 carbon atoms, each optionally having 1 or 2 substituent(s) selected from halogen atom, hydroxy group, nitro group, optionally halogenated alkyl group having 1 to 6 carbon atom(s), alkoxy group having  
30 1 to 6 carbon atom(s), aromatic heterocyclic group (e.g., quinolyl and the like) and cycloalkyl group having 3 to 10 carbon atoms;

X is a bond or -O-; and

L is C<sub>1-10</sub> alkylene.

35 [compound B]

A compound wherein ring A is a benzene ring

- optionally having 1 or 2 substituent(s) selected from
- 1) a cyano group;
  - 2) a C<sub>1-10</sub> alkyl group (preferably ethyl) or a C<sub>2-10</sub> alkenyl group (preferably ethenyl), each optionally
  - 5 substituted by carbamoyl group or carboxyl group;
  - 3) an optionally substituted hydroxy group [preferably alkoxy group having 1 to 10 carbon atom(s) (preferably methoxy, isopropoxy) optionally having 1 to 3 substituent(s) selected from carbamoyl group, carboxyl
  - 10 group and alkoxycarbonyl group having 2 to 5 carbon atoms (preferably methoxycarbonyl) ; hydroxy group; aralkyloxy group having 7 to 13 carbon atoms (preferably benzyloxy)] [more preferably carbamoylmethoxy];
  - 4) an acyl group [preferably C<sub>1-6</sub> alkyl-carbonyl
  - 15 (preferably acetyl), carbamoyl, mono- or di-(C<sub>1-6</sub> alkyl optionally having 1 to 3 substituent(s) selected from halogen atom and C<sub>1-6</sub> alkoxy-carbonyl)-carbamoyl (preferably methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, dimethylcarbamoyl,
  - 20 trifluoroethylcarbamoyl, ethoxycarbonylmethylcarbamoyl and the like), C<sub>3-10</sub> cycloalkyl-carbamoyl (preferably cyclopropylcarbamoyl), C<sub>7-13</sub> aralkyl-carbamoyl (preferably benzylcarbamoyl), nitrogen-containing heterocycle-carbonyl optionally substituted by hydroxy
  - 25 (preferably pyrrolidinylcarbonyl, piperidinocarbonyl), C<sub>1-6</sub> alkylsulfonyl (preferably methylsulfonyl), C<sub>1-6</sub> alkylsulfinyl (preferably methylsulfinyl), carboxyl, C<sub>1-6</sub> alkoxy-carbonyl (preferably methoxycarbonyl), thiocarbamoyl];
  - 30 5) an optionally substituted amino group (preferably carbamoylamino);
  - 6) an optionally substituted thiol group [preferably alkylthio group having 1 to 10 carbon atom(s) optionally substituted by carbamoyl group (preferably methylthio);
  - 35 7) an optionally substituted heterocyclic group [preferably aromatic heterocyclic group (preferably

furyl, thienyl, oxazolyl, oxadiazolyl, thiazolyl, tetrazolyl, pyridyl, pyrrolyl, triazolyl) or non-aromatic heterocyclic group (preferably dioxoisindole, 5-oxooxadiazol-3-yl, 5-oxothiadiazol-3-yl), each  
5 optionally having 1 or 2 substituent(s) selected from C<sub>1-6</sub> alkyl group optionally substituted by 1 to 3 halogen atom(s) (preferably methyl, trifluoromethyl), carboxyl group, alkoxycarbonyl group having 2 to 8 carbon atoms (preferably ethoxycarbonyl), cyano group, carbamoyl  
10 group, amino group, mono- or di-C<sub>2-10</sub> alkanoylamino group (e.g., acetylamino, isopentanoylamino), C<sub>1-10</sub> alkoxy-carbonylamino group (e.g., methoxycarbonylamino), carbamoylamino group, mono- or di-C<sub>1-10</sub> alkyl-carbamoylamino group (e.g., methylcarbamoylamino,  
15 dimethylcarbamoylamino), C<sub>6-14</sub> aryl-carbonylamino group (e.g., benzoylamino), C<sub>3-10</sub> cycloalkyl-carbonylamino group, C<sub>7-13</sub> aralkyloxy-carbonylamino group, mono- or di-C<sub>1-10</sub> alkylsulfonylamino group (e.g., methylsulfonylamino, dimethylsulfonylamino), C<sub>6-14</sub> arylsulfonylamino group and  
20 C<sub>1-6</sub> alkoxy-carbamoylamino group (e.g., methoxycarbamoylamino); and  
8) an amidino group;  
R<sup>1</sup> is an alkyl group having 4 to 10 carbon atoms (preferably isobutyl, neopentyl) or a cycloalkylalkyl  
25 group having 4 to 10 carbon atoms (preferably cyclopropylmethyl);  
R<sup>2</sup> is an aryl group having 6 to 14 carbon atoms (preferably phenyl) optionally having 1 or 2 substituent(s) selected from halogen atom (preferably  
30 fluorine, chlorine) and C<sub>1-6</sub> alkyl (preferably methyl);  
X is a bond; and  
L is C<sub>1-10</sub> alkylene (preferably -CH<sub>2</sub>-).  
[compound C]

A compound wherein ring A is is a benzene ring  
35 optionally having 1 or 2 substituent(s) selected from  
1) a C<sub>1-10</sub> alkyl group (preferably ethyl) or a C<sub>2-10</sub>

- alkenyl group (preferably ethenyl), each optionally substituted by alkoxycarbonyl group having 2 to 8 carbon atoms (preferably ethoxycarbonyl) or carbamoyl group;
- 2) an optionally substituted hydroxy group [preferably alkoxy group having 1 to 10 carbon atom(s) (preferably methoxy) optionally substituted by carbamoyl group; more preferably carbamoylmethoxy];
- 3) an acyl group (preferably carbamoyl, thiocarbamoyl, carboxyl);
- 4) an optionally substituted heterocyclic group [preferably aromatic heterocyclic group (preferably furyl, thienyl, oxazolyl, oxadiazolyl, thiazolyl, tetrazolyl, pyridyl, pyrrolyl, triazolyl) or non-aromatic heterocyclic group (preferably 5-oxooxadiazol-3-yl), each optionally having 1 or 2 substituent(s) selected from C<sub>1-6</sub> alkyl group (preferably methyl), carboxyl group, alkoxycarbonyl group having 2 to 8 carbon atoms (preferably ethoxycarbonyl), cyano group, carbamoyl group, amino group, mono- or di-C<sub>2-10</sub> alkanoylamino group (e.g., acetylamino, isopentanoylamino), C<sub>1-10</sub> alkoxy-carbonylamino group (e.g., methoxycarbonylamino), carbamoylamino group, mono- or di-C<sub>1-10</sub> alkyl-carbamoylamino group (e.g., methylcarbamoylamino, dimethylcarbamoylamino), C<sub>6-14</sub> aryl-carbonylamino group (e.g., benzoylamino), C<sub>3-10</sub> cycloalkyl-carbonylamino group, C<sub>7-13</sub> aralkyloxy-carbonylamino group, mono- or di-C<sub>1-10</sub> alkylsulfonylamino group (e.g., methylsulfonylamino, dimethylsulfonylamino), C<sub>6-14</sub> arylsulfonylamino group and C<sub>1-6</sub> alkoxy-carbamoylamino group (e.g., methoxycarbamoylamino)];
- R<sup>1</sup> is an alkyl group having 4 to 10 carbon atoms (preferably isobutyl, neopentyl) or a cycloalkylalkyl group having 4 to 10 carbon atom(s) (preferably cyclopropylmethyl);
- R<sup>2</sup> is an alkyl group having 1 to 10 carbon atom(s), which is optionally substituted by 1 to 3 halogen

atom(s) (preferably butyl);

X is -O-; and

L is C<sub>1-10</sub> alkylene (preferably -CH<sub>2</sub>-).

Preferable examples of compound (I) include  
5 compounds shown by the following formula.

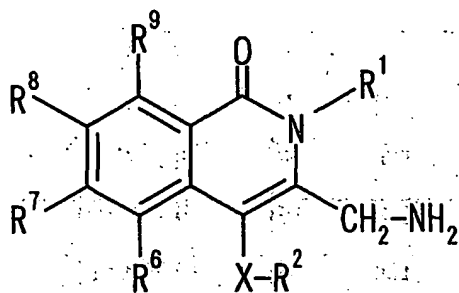


Table 1

No.	X	R <sup>1</sup>	R <sup>2</sup>	R <sup>6</sup>	R <sup>7</sup>	R <sup>8</sup>	R <sup>9</sup>
1	O	neo-Pent	n-Bu	H	EtO—	H	H
2	O	neo-Pent	n-Bu	H	H	F	H
3	O	neo-Pent	n-Bu	H	F	H	H
4	O	Me	Me	H	Cl	H	H
5	O	Me	Me	H	H	Cl	H
6	O	Me	i-Pr	H	Cl	H	H
7	O	Me	n-Bu	H	Cl	H	H
8	O	Me	PhCH <sub>2</sub> —	H	Cl	H	H
9	O	Me	a)	H	Cl	H	H
10	O	Me	PhCH <sub>2</sub> CH <sub>2</sub> —	H	Cl	H	H
11	O	Me	b)	H	Cl	H	H
12	—	Me	Ph	H	H	Cl	H
13	O	Me	n-Pr	H	Cl	H	H
14	O	Me	c)	H	Cl	H	H
15	O	Me	4-NO <sub>2</sub> Ph	H	Cl	H	H
16	—	Me	4-MeOPh	H	Cl	H	H
17	—	Me	3-MeOPh	H	Cl	H	H
18	—	Me	4-HOPh	H	Cl	H	H
19	—	Me	3-HOPh	H	Cl	H	H
20	—	Me	4-FPh	H	Cl	H	H
21	—	Me	4-F <sub>3</sub> CPh	H	Cl	H	H
22	—	Me	Ph	H	Cl	Cl	H
23	—	Me	3-NO <sub>2</sub> Ph	H	Cl	H	H
24	—	Me	3-NH <sub>2</sub> Ph	H	Cl	H	H
25	O	n-Pr	n-Bu	H	Cl	H	H



Table 2

No.	X	R <sup>1</sup>	R <sup>2</sup>	R <sup>6</sup>	R <sup>7</sup>	R <sup>8</sup>	R <sup>9</sup>
26	O	i-Bu	n-Bu	H	Cl	Cl	H
27	O	neo-Pent	n-Bu	H	Cl	Cl	H
28	O	PhCH <sub>2</sub> -	n-Bu	H	Cl	Cl	H
29	O	i-Bu	n-Pent	H	Cl	Cl	H
30	O	i-Pr	n-Bu	H	Cl	Cl	H
31	O	c-Pr	n-Bu	H	Cl	Cl	H
32	O	c-PrCH <sub>2</sub> -	n-Bu	H	Cl	Cl	H
33	O	i-Pent	n-Bu	H	Cl	Cl	H
34	O	neo-Pent	i-Bu	H	Cl	Cl	H
35	O	d)	n-Bu	H	Cl	Cl	H
36	O	Me	n-Bu	H	Cl	Cl	H
41	O	e)	n-Bu	H	Cl	Cl	H
42	O	f)	n-Bu	H	Cl	Cl	H
43	O	g)	n-Bu	H	Cl	Cl	H
44	O	h)	n-Bu	H	Cl	Cl	H
45	O	i)	n-Bu	H	Cl	Cl	H
46	O	neo-Pent	n-Bu	H	H	H	H
47	O	j)	n-Bu	H	Cl	Cl	H
48	O	MeOCH <sub>2</sub> CH <sub>2</sub> -	n-Bu	H	Cl	Cl	H
49	O	neo-Pent	MeOCH <sub>2</sub> CH <sub>2</sub> -	H	H	H	H
50	O	neo-Pent	n-Bu	H	H	Me	H

Table 3

No.	X	R <sup>1</sup>	R <sup>2</sup>	R <sup>6</sup>	R <sup>7</sup>	R <sup>8</sup>	R <sup>9</sup>
51	O	neo-Pent	n-Bu	H	Me	H	H
52	O	neo-Pent	n-Bu	H	H	CF <sub>3</sub>	H
53	O	neo-Pent	n-Bu	H	CF <sub>3</sub>	H	H
54	O	k)	n-Bu	H	Cl	Cl	H
55	O	l)	n-Bu	H	Cl	Cl	H
57	O	neo-Pent	n-Bu	H	MeO—	H	H
58	O	neo-Pent	n-Bu	H	PhCH <sub>2</sub> O—	H	H
59	O	neo-Pent	n-Bu	H	HO—	H	H
60	O	neo-Pent	n-Bu	H	n-PrO—	H	H
61	O	neo-Pent	n-Bu	H	n-BuO—	H	H
62	O	neo-Pent	n-Bu	H	MeOCH <sub>2</sub> CH <sub>2</sub> O—	H	H
63	O	neo-Pent	n-Bu	H	H	PhCH <sub>2</sub> O	H
64	O	neo-Pent	n-Bu	H	H	HO—	H
65	O	neo-Pent	n-Bu	H	H	MeO—	H
66	O	neo-Pent	n-Bu	H	H	EtO—	H
67	O	neo-Pent	n-Bu	H	H	n-PrO	H
68	O	neo-Pent	n-Bu	H	H	n-BuO	H
69	O	neo-Pent	n-Bu	MeO	MeO—	H	H
70	O	neo-Pent	n-Bu	H	MeO—	MeO—	H
74	O	i-Bu	n-Bu	H	Br	H	H
75	O	i-Bu	n-Bu	H	MeOCO—	H	H

Table 4

No.	X	R <sup>1</sup>	R <sup>2</sup>	R <sup>6</sup>	R <sup>7</sup>	R <sup>8</sup>	R <sup>9</sup>
76	O	i-Bu	n-Bu	H	HOCO—	H	H
77	O	i-Bu	n-Bu	H	H <sub>2</sub> NCO—	H	H
78	O	i-Bu	n-Bu	H	NC—	H	H
79	O	i-Bu	n-Bu	H	HOCH <sub>2</sub> —	H	H
80	O	i-Bu	n-Bu	H	MeNHCONH—	H	H
81	O	i-Bu	n-Bu	H	MeOCONH—	H	H
82	O	i-Bu	n-Bu	H	NH <sub>2</sub> —	H	H
83	O	neo-Pent	n-Bu	H	Br	H	H
84	O	neo-Pent	n-Bu	H	MeOCO—	H	H
85	O	neo-Pent	n-Bu	H	HOCO—	H	H
86	O	neo-Pent	n-Bu	H	H <sub>2</sub> NCO—	H	H
87	O	neo-Pent	n-Bu	H	NC—	H	H
88	O	i-Bu	n-Bu	H	AcNH—	H	H
89	O	i-Bu	n-Bu	H	EtCONH—	H	H
90	O	i-Bu	n-Bu	H	m)	H	H
91	O	i-Bu	n-Bu	H	n)	H	H
92	O	i-Bu	n-Bu	H	o)	H	H
93	O	i-Bu	n-Bu	H	MsNH—	H	H
94	O	i-Bu	n-Bu	H	PhSO <sub>2</sub> NH—	H	H
95	O	neo-Pent	n-Bu	H	p)	H	H
96	O	neo-Pent	n-Bu	H	i-PrO—	H	H
97	O	neo-Pent	n-Bu	H	CF <sub>3</sub> CH <sub>2</sub> O—	H	H
98	O	neo-Pent	n-Bu	H	q)	H	H
99	O	neo-Pent	n-Bu	H	r)	H	H
100	O	neo-Pent	n-Bu	H	i-BuO—	H	H

Table 5

No.	X	R <sup>1</sup>	R <sup>2</sup>	R <sup>6</sup>	R <sup>7</sup>	R <sup>8</sup>	R <sup>9</sup>
101	O	neo-Pent	n-Bu	H	s)	H	H
102	O	neo-Pent	n-Bu	H	t)	H	H
103	O	neo-Pent	n-Bu	H	u)	H	H
104	O	neo-Pent	n-Bu	H	EtOCOCH <sub>2</sub> O-	H	H
105	O	neo-Pent	n-Bu	H	v)	H	H
106	-	i-Bu	Ph	H	Br	H	H
107	-	i-Bu	Ph	H	MeOCO-	H	H
108	-	i-Bu	Ph	H	HOCO-	H	H
109	-	i-Bu	Ph	H	H <sub>2</sub> NCO-	H	H
110	-	i-Bu	Ph	H	CbzNH-	H	H
111	-	i-Bu	Ph	H	NH <sub>2</sub> -	H	H
112	-	i-Bu	Ph	H	AcNH-	H	H
113	-	Et	Ph	H	Cl	H	H
114	-	n-Pr	Ph	H	Cl	H	H
115	-	n-Bu	Ph	H	Cl	H	H
116	-	Me	Ph	H	Br	H	H
117	-	n-Pent	Ph	H	Cl	H	H
118	-	i-Bu	Ph	H	Cl	H	H
119	-	c-HexCH <sub>2</sub> -	Ph	H	Cl	H	H
120	-	i-Bu	4-FPh	H	Cl	Cl	H
121	-	i-Bu	Ph	H	Cl	Cl	H
122	-	neo-Pent	Ph	H	Cl	H	H
123	-	i-Bu	Ph	H	H	H	H
124	-	i-Bu	4-ClPh	H	H	H	H
125	-	i-Bu	4-MePh	H	H	H	H

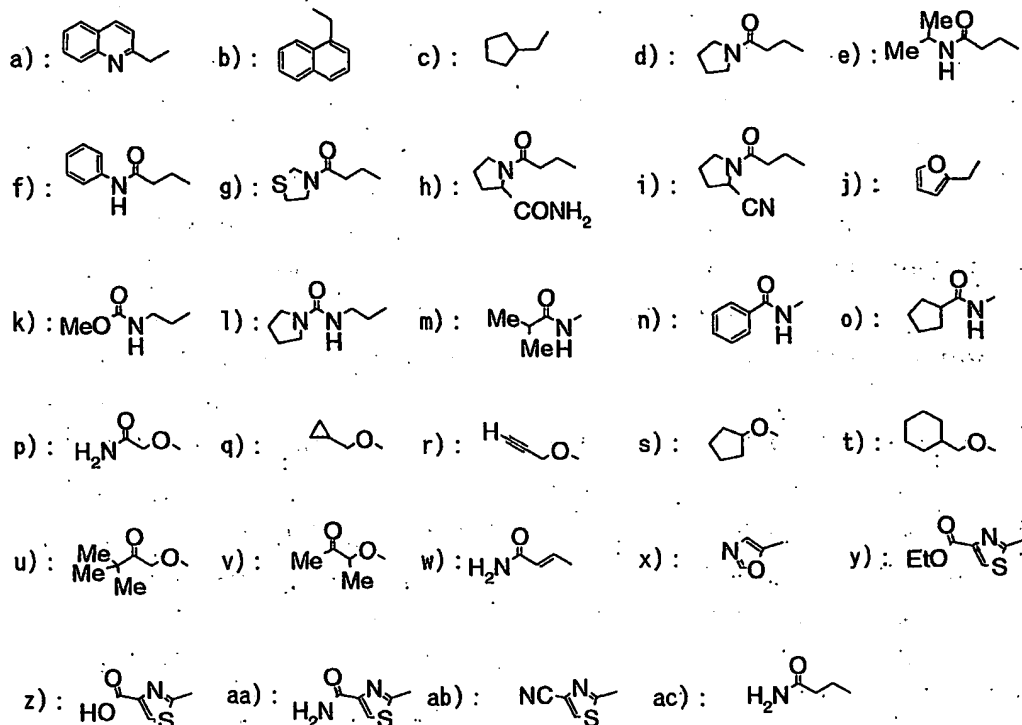
Table 6

No.	X	R <sup>1</sup>	R <sup>2</sup>	R <sup>6</sup>	R <sup>7</sup>	R <sup>8</sup>	R <sup>9</sup>
126	-	i-Bu	Ph	H	F	H	H
127	-	i-Bu	Ph	H	MeO-	H	H
128	-	i-Bu	Ph	H	EtO-	H	H
129	-	i-Bu	Ph	H	n-PrO-	H	H
130	-	i-Bu	Ph	H	MeO-	MeO-	H
131	-	i-Bu	4-FPh	H	MeOCO-	H	H
132	-	i-Bu	4-FPh	H	HOCO-	H	H
133	-	i-Bu	4-FPh	H	H <sub>2</sub> NCO-	H	H
134	-	i-Bu	4-FPh	H	AcNH-	H	H
135	-	i-Bu	4-FPh	H	EtO-	H	H
136	-	i-Bu	4-FPh	H	p)	H	H
137	-	i-Bu	2-FPh	H	MeOCO-	H	H
138	-	i-Bu	2-FPh	H	HOCO-	H	H
139	-	i-Bu	2-FPh	H	H <sub>2</sub> NCO-	H	H
140	-	i-Bu	2-FPh	H	AcNH-	H	H
141	-	i-Bu	2-FPh	H	p)	H	H
142	-	i-Bu	3-FPh	H	MeOCO-	H	H
143	-	i-Bu	3-FPh	H	HOCO-	H	H
144	-	i-Bu	3-FPh	H	H <sub>2</sub> NCO-	H	H
145	-	i-Bu	3-FPh	H	AcNH-	H	H
146	-	i-Bu	3-FPh	H	EtO-	H	H
147	-	i-Bu	Ph	H	MeNHCONH-	H	H
148	-	i-Bu	Ph	H	Me <sub>2</sub> NCONH-	H	H
149	-	i-Bu	Ph	H	H <sub>2</sub> NCONH-	H	H
150	O	i-Bu	CF <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> -	H	p)	H	H

Table 7

No.	X	R <sup>1</sup>	R <sup>2</sup>	R <sup>6</sup>	R <sup>7</sup>	R <sup>8</sup>	R <sup>9</sup>
151	O	c-PrCH <sub>2</sub> -	n-Bu	H	H <sub>2</sub> NCO-	H	H
152	O	c-PrCH <sub>2</sub> -	n-Bu	H	p)	H	H
153	O	c-PrCH <sub>2</sub> -	n-Bu	H	w)	H	H
154	O	i-Bu	n-Bu	H	p)	H	H
155	O	i-Bu	n-Bu	H	w)	H	H
156	-	i-Bu	Ph	H	NC-	H	H
157	-	i-Bu	Ph	H	MeNHCO-	H	H
158	-	i-Bu	Ph	H	p)	H	H
159	-	i-Bu	Ph	H	w)	H	H
160	O	neo-Pent	n-Bu	H	w)	H	H
161	O	c-PrCH <sub>2</sub> -	n-Bu	H	x)	H	H
162	O	i-Bu	n-Bu	H	x)	H	H
163	-	i-Bu	Ph	H	x)	H	H
164	O	i-Bu	n-Bu	H	y)	H	H
165	-	i-Bu	Ph	H	y)	H	H
166	O	i-Bu	n-Bu	H	z)	H	H
167	-	i-Bu	Ph	H	z)	H	H
168	O	i-Bu	n-Bu	H	aa)	H	H
169	-	i-Bu	Ph	H	aa)	H	H
170	O	i-Bu	n-Bu	H	ab)	H	H
171	-	i-Bu	Ph	H	ab)	H	H
172	-	i-Bu	4-MePh	H	p)	H	H
173	-	i-Bu	4-ClPh	H	p)	H	H
174	-	i-Bu	4-MePh	H	z)	H	H
175	-	i-Bu	4-ClPh	H	z)	H	H
176	-	i-Bu	4-MePh	H	ac)	H	H

The symbols in the Tables mean the following:



5

Me: methyl, Et: ethyl, CF<sub>3</sub>: trifluoromethyl,  
 neo-Pent: neopentyl, n-Bu: n-butyl, i-Bu: isobutyl,  
 i-Pr: isopropyl, Ph: phenyl, n-Pr: n-propyl,  
 4-NO<sub>2</sub>Ph: 4-nitrophenyl, 4-MeOPh: 4-methoxyphenyl,  
 10 4-MePh: 4-methylphenyl, 4-HOPh: 4-hydroxyphenyl,  
 3-MeOPh: 3-methoxyphenyl, 3-HOPh: 3-hydroxyphenyl,  
 4-FPh: 4-fluorophenyl, 4-CF<sub>3</sub>Ph: 4-trifluoromethylphenyl,  
 3-NO<sub>2</sub>Ph: 3-nitrophenyl, 3-NH<sub>2</sub>Ph: 3-aminophenyl,  
 n-Pent: n-pentyl, i-Pent: isopentyl, c-Pr:  
 15 cyclopropyl,  
 c-Hex: cyclohexyl, 4-ClPh: 4-chlorophenyl,  
 2-FPh: 2-fluorophenyl, 3-FPh: 3-fluorophenyl,  
 Cbz: benzyloxycarbonyl, Ac: acetyl, Ms:

## methanesulfonyl

More Preferable examples of compound (I) include:

- 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carbonitrile;  
5 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carboxylic acid;  
2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carboxamide;  
ethyl 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-  
10 dihydro-6-isoquinolyl]-1,3-thiazole-4-carboxylate;  
(E)-3-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-2-propenamide;  
(E)-3-[3-(aminomethyl)-2-isobutyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]-2-propenamide;  
15 3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxamide;  
2-[[3-(aminomethyl)-2-isobutyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]oxy]acetamide; and the like.

- As a salt of the compound of the formula (I)  
20 (hereinafter sometimes to be abbreviated as compound (I)), pharmacologically acceptable salt is preferable. Examples of such salt include salt with inorganic base, salt with organic base, salt with inorganic acid, salt with organic acid, salt with basic or acidic amino acid  
25 and the like.

- Preferable examples of the salt with inorganic base include alkali metal salts such as sodium salt, potassium salt and the like; alkaline earth metal salts such as calcium salt, magnesium salt and the like;  
30 aluminum salt; ammonium salt and the like.

- Preferable examples of the salt with organic base include a salt with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N-  
35 dibenzylethylenediamine or the like.

Preferable examples of the salt with inorganic acid



include a salt with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid or the like.

Preferable examples of the salt with organic acid include a salt with formic acid, acetic acid,  
5 trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid or the like.

Preferable examples of the salt with basic amino  
10 acid include a salt with arginine, lysin, ornithine or the like.

Preferable examples of the salt with acidic amino acid include a salt with aspartic acid, glutamic acid or the like.

15 Of the above-mentioned salts, sodium salt, potassium salt, hydrochloride and the like are preferable.

A prodrug of compound (I) is a compound that converts to compound (I) due to the reaction of enzyme, gastric acid and the like under the physiological  
20 conditions in the body. That is, a compound that converts to compound (I) by enzymatic oxidation, reduction, hydrolysis and the like, and a compound that converts to compound (I) by hydrolysis and the like by  
25 gastric acid and the like. A prodrug of compound (I) is exemplified by a compound wherein an amino group of compound (I) is acylated, alkylated, phosphorylated (e.g., compound where amino group of compound (I) is eicosanoylated, alanylated, pentylaminocarbonylated, (5-  
30 methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylated, tetrahydrofuranylated, pyrrolidylmethylated, pivaloyloxymethylated, tert-butylated and the like); compound wherein a hydroxy group of compound (I) is acylated, alkylated, phosphorinated, borated (e.g.,  
35 compound where hydroxy group of compound (I) is acetylated, palmitoylated, propanoylated, pivaloylated,

succinilated, fumarinated, alanilated,  
dimethylaminomethylcarbonylated and the like); compound  
wherein a carboxyl group of compound (I) is esterified  
or amidated (e.g., compound where carboxyl group of  
5 compound (I) is ethyl esterified, phenyl esterified,  
carboxymethyl esterified, dimethylaminomethyl esterified,  
pivaloyloxymethyl esterified, ethoxycarbonyloxyethyl  
esterified, phthalidyl esterified, (5-methyl-2-oxo-1,3-  
dioxolen-4-yl)methyl esterified,  
10 cyclohexyloxycarbonyethyl esterified, methylamidated and  
the like) and the like. These compounds can be produced  
from compound (I) by a method known *per se*.

A prodrug of compound (I) may be a compound that  
converts to compound (I) under physiological conditions  
15 as described in Development of pharmaceutical products,  
vol. 7, Molecule Design, 163-198, Hirokawa Shoten (1990).

The compound (I) may be labeled with isotope (e.g.,  
 $^3\text{H}$ ,  $^{14}\text{C}$ ,  $^{35}\text{S}$ ,  $^{125}\text{I}$  and the like) and the like.

The compound (I) may be an anhydride or a hydrate.

20 The compound (I), a salt thereof and a prodrug  
thereof (hereinafter sometimes to be simply referred to  
as the compound of the present invention) show low  
toxicity and can be used as an agent for the prophylaxis  
or treatment of various diseases to be mentioned later  
25 for mammal (e.g., human, mouse, rat, rabbit, dog, cat,  
cattle, horse, swine, simian and the like) by admixing  
with a pharmacologically acceptable carrier and the like  
to give a pharmaceutical composition.

Here, various organic or inorganic carriers  
30 conventionally used as materials for pharmaceutical  
preparations are used as a pharmacologically acceptable  
carrier, which are added as excipient, lubricant, binder,  
disintegrant for solid preparations; and solvent,  
dissolution aids, suspending agent, isotonicity agent,  
35 buffer, soothing agent and the like for liquid  
preparations. Where necessary, additive for

pharmaceutical preparations such as preservative, antioxidant, coloring agent, sweetening agent and the like can be used.

Preferable examples of the excipient include

- 5 lactose, sucrose, D-mannitol, D-sorbitol, pregelatinized starch, dextrin, crystalline cellulose, low-substituted hydroxypropylcellulose, sodium carboxymethylcellulose, gum arabic, dextrin, pullulan, light silicic anhydride, synthetic aluminum silicate, magnesium aluminate  
10 metasilicate and the like.

Preferable examples of the lubricant include magnesium stearate, calcium stearate, talc, colloidal silica and the like.

Preferable examples of the binder include

- 15 pregelatinized starch, saccharose, gelatin, gum arabic, methylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, crystalline cellulose, sucrose, D-mannitol, trehalose, dextrin, pullulan, hydroxypropyl cellulose, hydroxypropylmethylcellulose,  
20 polyvinylpyrrolidone and the like.

Preferable examples of the disintegrant include lactose, sucrose, starch, carboxymethylcellulose, calcium carboxymethylcellulose, sodium crosscarmellose, sodium carboxymethyl starch, light silicic anhydride,  
25 low-substituted hydroxypropylcellulose and the like.

Preferable examples of the solvent include water for injection, physiological brine, Ringer's solution, alcohol, propylene glycol, polyethylene glycol, sesame oil, corn oil, olive oil, cottonseed oil and the like.

- 30 Preferable examples of the dissolution aids include polyethylene glycol, propylene glycol, D-mannitol, trehalose, benzyl benzoate, ethanol, Tris aminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, sodium salicylate, sodium acetate and the like.

- 35 Preferable examples of the suspending agent include surfactants such as stearyltriethanolamine, sodium

lauryl sulfate, lauryl aminopropionate, lecithin, benzalkonium chloride, benzethonium chloride, monostearic glyceride and the like; hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, sodium  
5 carboxymethylcellulose, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and the like; polysorbates, polyoxyethylene hydrogenated castor oil and the like.

Preferable examples of the isotonicity agent  
10 include sodium chloride, glycerol, D-mannitol, D-sorbitol, glucose and the like.

Preferable examples of the buffer include phosphate buffer, acetate buffer, carbonate buffer, citrate buffer, and the like.

15 Preferable examples of the soothing agent include benzyl alcohol and the like.

Preferable examples of the preservative include p-oxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid and  
20 the like.

Preferable examples of the antioxidant include sulfite, ascorbate and the like.

Preferable examples of the coloring agent include water-soluble edible tar pigment (e.g., foodcolors such  
25 as Food Color Red Nos. 2 and 3, Food Color Yellow Nos. 4 and 5, Food Color Blue Nos. 1 and 2 and the like, water insoluble lake pigment (e.g., aluminum salt of the aforementioned water-soluble edible tar pigment and the like), natural pigments (e.g., beta carotene, chlorophyll,  
30 red iron oxide etc.) and the like.

Preferable examples of the sweetening agent include saccharin sodium, dipotassium glycyrrhizinate, aspartame, stevia and the like.

The dosage form of the aforementioned  
35 pharmaceutical composition may be, for example, oral agents such as tablets (inclusive of sublingual tablets

and orally disintegrable tablets), capsules (inclusive of soft capsules and micro capsules), granules, powders, troches, syrups, emulsions, suspensions and the like; or parenteral agents such as injections (e.g., subcutaneous  
5 injections, intravenous injections, intramuscular injections, intraperitoneal injections, drip infusions and the like), external agents (e.g., transdermal preparations, ointments and the like), suppositories (e.g., rectal suppositories, vaginal suppositories and  
10 the like), pellets, nasal preparations, pulmonary preparations (inhalations), ophthalmic preparations and the like. These may be administered safely via oral or parenteral route. These agents may be controlled-release preparations such as rapid-release preparations  
15 and sustained-release preparations (e.g., sustained-release microcapsules).

The pharmaceutical composition can be produced according to a method conventionally used in the field of pharmaceutical preparation, such as the method  
20 described in Japan Pharmacopoeia and the like. The specific production methods of the pharmaceutical preparation are described in detail in the following.

While the content of the compound of the present invention in the pharmaceutical composition varies  
25 depending on dosage form, dose of the compound of the present invention and the like, it is, for example, about 0.1-100 wt%.

For example, an oral agent is produced by adding, to the active ingredient, excipient (e.g., lactose,  
30 sucrose, starch, D-mannitol and the like), disintegrant (e.g., calcium carboxymethylcellulose and the like), binder (e.g., pregelatinated starch, gum arabic, carboxymethylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone and the like), lubricant (e.g.,  
35 talc, magnesium stearate, polyethylene glycol 6000 and the like) and the like, compression-shaping the mixture,

and where necessary, coating the same using a coating base for masking of taste, enteric property or sustained release according to a method known per se.

Examples of the coating base include a sugar-  
5 coating base, a water-soluble film coating base, an enteric film coating base, a sustained release film coating base and the like.

As a sugar-coating base, sucrose may be used, along with one or two species selected from talc, precipitated  
10 calcium carbonate, gelatin, gum arabic, pullulan, carnauba wax and the like.

As a water-soluble film coating base, for example, cellulose polymers such as hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose,  
15 methylhydroxyethylcellulose and the like; synthetic polymers such as polyvinyl acetal diethylaminoacetate, aminoalkyl methacrylate copolymer E [Eudragit E, trademark, Rohm Pharma], polyvinylpyrrolidone and the like; polysaccharides such as pullulan and the like; and  
20 the like are used.

As a enteric film coating base, for example, cellulose polymers such as hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, carboxymethylethylcellulose, acetic phthalic  
25 cellulose and the like; acrylic acid polymers such as methacrylic acid copolymer L [Eudragit L, trademark, Rohm Pharma], methacrylic acid copolymer LD [Eudragit L-30D55, trademark, Rohm Pharma], methacrylic acid copolymer S [Eudragit S, trademark, Rohm Pharma] and the  
30 like; naturally occurring substance such as shellac and the like; and the like are used.

As a sustained release film coating base, for example, cellulose polymers such as ethylcellulose and the like; acrylic acid polymers such as aminoalkyl  
35 methacrylate copolymer RS [Eudragit RS, trademark, Rohm Pharma], ethyl acrylate-methyl methacrylate copolymer

suspension [Eudragit NE, trademark, Rohm Pharma] and the like, and the like are used.

Two or more kinds of the above-mentioned coating bases may be mixed in an appropriate ratio for use. In addition, a light shielding agent such as titanium oxide, iron tri or dioxide and the like may be used during coating.

An injection is produced by dissolving, suspending or emulsifying an active ingredient in an aqueous solvent (e.g., distilled water, physiological saline, Ringer's solution and the like) or an oily solvent (e.g., plant oil such as olive oil, sesame oil, cottonseed oil, corn oil and the like, propylene glycol and the like) and the like, together with a dispersing agent (e.g., polysorbate 80, polyoxyethylene hydrogenated castor oil 60 and the like), polyethylene glycol, carboxymethylcellulose, sodium alginate and the like), preservative (e.g., methylparaben, propylparaben, benzyl alcohol, chlorobutanol, phenol and the like), isotonicity agent (e.g., sodium chloride, glycerol, D-mannitol, D-sorbitol, glucose and the like) and the like.

In this step, dissolution aids (e.g., sodium salicylate, sodium acetate and the like), stabilizers (e.g., human serum albumin and the like), soothing agents (e.g., benzyl alcohol and the like) and the like may be used on demand.

The compound of the present invention and the pharmaceutical agent of the present invention show low toxicity, cause fewer side effects and can be used as an agent for the prophylaxis or treatment or diagnosis of various diseases to be mentioned later for mammal (e.g., human, cattle, horse, dog, cat, simian, mouse, rat, especially human).

The compound of the present invention and the pharmaceutical agent of the present invention have a superior peptidase inhibitory activity and can suppress

peptidase-caused degradation of a physiologically active substance such as peptide hormones, cytokines, neurotransmitters and the like.

Examples of the peptide hormones include glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2), GIP, growth hormone release hormone (GHRH) and the like.

Examples of the cytokines include chemokine such as RANTES and the like.

Examples of the neurotransmitters include  
10 neuropeptide Y and the like.

Examples of the peptidase include EC 3.4.11.1 (Leucyl aminopeptidase), EC 3.4.11.2 (Membrane alanine aminopeptidase), EC 3.4.11.3 (Cystinyl aminopeptidase), EC 3.4.11.4 (Tripeptide aminopeptidase), EC 3.4.11.5  
15 (Prolyl aminopeptidase), EC 3.4.11.6 (Aminopeptidase B), EC 3.4.11.7 (Glutamyl aminopeptidase), EC 3.4.11.9 (Xaa-Pro aminopeptidase), EC 3.4.11.10 (Bacterial leucyl aminopeptidase), EC 3.4.11.13 (Clostridial aminopeptidase), EC 3.4.11.14 (Cytosol alanyl  
20 aminopeptidase), EC 3.4.11.15 (Lysyl aminopeptidase), EC 3.4.11.16 (Xaa-Trp aminopeptidase), EC 3.4.11.17 (Tryptophanyl aminopeptidase), EC 3.4.11.18 (Methionyl aminopeptidase), EC 3.4.11.19 (D-stereospecific aminopeptidase), EC 3.4.11.20 (Aminopeptidase Ey), EC  
25 3.4.11.21 (Aspartyl aminopeptidase), EC 3.4.11.22 (Aminopeptidase I), EC 3.4.13.3 (Xaa-His dipeptidase), EC 3.4.13.4 (Xaa-Arg dipeptidase), EC 3.4.13.5 (Xaa-methyl-His dipeptidase), EC 3.4.13.7 (Glu-Glu dipeptidase), EC 3.4.13.9 (Xaa-Pro dipeptidase), EC  
30 3.4.13.12 (Met-Xaa dipeptidase), EC 3.4.13.17 (Non-stereospecific dipeptidase), EC 3.4.13.18 (Cytosol nonspecific dipeptidase), EC 3.4.13.19 (Membrane dipeptidase), EC 3.4.13.20 (Beta-Ala-His dipeptidase), EC 3.4.14.1 (Dipeptidyl-peptidase I), EC 3.4.14.2  
35 (Dipeptidyl-peptidase II), EC 3.4.14.4 (Dipeptidyl-peptidase III), EC 3.4.14.5 (Dipeptidyl-peptidase IV),



EC 3.4.14.6 (Dipeptidyl-dipeptidase), EC 3.4.14.9 (Tripeptidyl-peptidase I), EC 3.4.14.10 (Tripeptidyl-peptidase II) and EC 3.4.14.11 (Xaa-Pro dipeptidyl-peptidase) as classified by International Union of  
5 Biochemistry and Molecular Biology (IUBMB), and the like.

Of these, EC 3.4.14.1, EC 3.4.14.2, EC 3.4.14.4, EC 3.4.14.5, EC 3.4.14.6, EC 3.4.14.9, EC 3.4.14.10 and EC 3.4.14.11 are preferable. Especially preferred is EC 3.4.14.5.

10 The compound of the present invention and the pharmaceutical agent of the present invention are useful as a prophylactic and therapeutic agent of diabetes (e.g., type 1 diabetes, type 2 diabetes, gestational diabetes and the like); prophylactic and therapeutic  
15 agent of hyperlipidemia (e.g., hypertriglyceridemia, hypercholesterolemia, low HDL lipemia, postprandial lipemia and the like); prophylactic and therapeutic agent of arteriosclerosis; prophylactic and therapeutic agent of impaired glucose tolerance [IGT]; an insulin  
20 secretagogue; and an agent for suppressing progress of impaired glucose tolerance into diabetes.

For diagnostic criteria of diabetes, Japan Diabetes Society reported new diagnostic criteria in 1999.

According to this report, diabetes is a condition  
25 showing any of a fasting blood glucose level (glucose concentration of intravenous plasma) of not less than 126 mg/dl, a 75 g oral glucose tolerance test (75 g OGTT) 2 h level (glucose concentration of intravenous plasma) of not less than 200 mg/dl, a non-fasting blood  
30 glucose level (glucose concentration of intravenous plasma) of not less than 200 mg/dl. A condition not falling under the above-mentioned diabetes, or "a condition showing a fasting blood glucose level (glucose concentration of intravenous plasma) of less than 110  
35 mg/dl or a 75 g oral glucose tolerance test (75 g OGTT) 2 h level (glucose concentration of intravenous plasma)

of less than 140 mg/dl" (normal type) is called a "borderline type".

In addition, ADA (American Diabetes Academy) reported new diagnostic criteria of diabetes in 1997 and  
5 WHO in 1998.

According to these reports, diabetes is a condition showing a fasting blood glucose level (glucose concentration of intravenous plasma) of not less than 126 mg/dl and a 75 g oral glucose tolerance test 2 h  
10 level (glucose concentration of intravenous plasma) of not less than 200 mg/dl.

According to the above-mentioned reports, impaired glucose tolerance is a condition showing a fasting blood glucose level (glucose concentration of intravenous  
15 plasma) of less than 126 mg/dl and a 75 g oral glucose tolerance test 2 h level (glucose concentration of intravenous plasma) of not less than 140 mg/dl and less than 200 mg/dl. According to the report of ADA, a condition showing a fasting blood glucose level (glucose  
20 concentration of intravenous plasma) of not less than 110 mg/dl and less than 126 mg/dl is called IFG (Impaired Fasting Glucose). According to the report of WHO, among the IFG (Impaired Fasting Glucose), a condition showing a 75g oral glucose tolerance test 2 h  
25 level (glucose concentration of intravenous plasma) of less than 140 mg/dl is called IFG (Impaired Fasting Glycemia).

The compound of the present invention and the pharmaceutical agent of the present invention can be  
30 also used as a prophylactic and therapeutic agent of diabetes, borderline type, impaired glucose tolerance, IFG (Impaired Fasting Glucose) and IFG (Impaired Fasting Glycemia), as determined according to the above-mentioned new diagnostic criteria. Moreover, the  
35 compound of the present invention and the pharmaceutical agent of the present invention can prevent progress of

borderline type, impaired glucose tolerance, IFG (Impaired Fasting Glucose) or IFG (Impaired Fasting Glycemia) into diabetes.

The compound of the present invention and the  
5 pharmaceutical agent of the present invention can be also used as a prophylactic and therapeutic agent of, for example, diabetic complications [e.g., neuropathy, nephropathy, retinopathy, cataract, macroangiopathy, osteopenia, hyperosmolar diabetic coma, infectious  
10 disease (respiratory infection, urinary tract infection, gastrointestinal infection, dermal soft tissue infections, inferior limb infection and the like), diabetic gangrene, xerostomia, hypacusis, cerebrovascular disorder, peripheral blood circulation  
15 disorder and the like], obesity, osteoporosis, cachexia (e.g., cancerous cachexia, tuberculous cachexia, diabetic cachexia, blood disease cachexia, endocrine disease cachexia, infectious disease cachexia or cachexia due to acquired immunodeficiency syndrome),  
20 fatty liver, hypertension, polycystic ovary syndrome, kidney disease (e.g., diabetic nephropathy, glomerular nephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, end stage kidney disease and the like), muscular dystrophy, myocardial infarction,  
25 angina pectoris, cerebrovascular accident (e.g., cerebral infarction, cerebral apoplexy), insulin resistance syndrome, Syndrome X, hyperinsulinemia, hyperinsulinemia-induced sensory disorder, tumor (e.g., leukemia, breast cancer, prostatic cancer, skin cancer  
30 and the like), irritable bowel syndrome, acute or chronic diarrhea, inflammatory diseases (e.g., chronic rheumatoid arthritis, spondylitis deformans, arthritis cleformans, lumbar pain, gout, postoperative or traumatic inflammation, remission of tumentia, neuralgia,  
35 pharyngolaryngitis, cystitis, hepatitis (inclusive of nonalcoholic steatohepatitis), pneumonia, pancreatitis,

inflammatory bowel disease, ulcerative colitis, gastric mucosal injury (inclusive of gastric mucosal injury caused by aspirin) and the like), visceral obesity syndrome and the like.

5       The compound of the present invention and the pharmaceutical agent of the present invention can be also used for decreasing visceral fat, suppressing visceral fat accumulation, improving glycometabolism, improving lipid metabolism, suppressing production of  
10 oxidized LDL, improving lipoprotein metabolism, improving coronary artery metabolism, prophylaxis and treatment of cardiovascular complication, prophylaxis and treatment of heart failure complication, lowering blood remnant, prophylaxis and treatment of anovulation,  
15 prophylaxis and treatment of hypertrichosis, prophylaxis and treatment of hyperandrogenemia, improving pancreatic ( $\beta$  cell) function, regeneration of pancreatic ( $\beta$  cell), promotion of pancreatic ( $\beta$  cell) regeneration, and the like.

20       The compound of the present invention and the pharmaceutical agent of the present invention can be also used for secondary prophylaxis and suppression of progression of the above-mentioned various diseases (e.g., cardiovascular event such as myocardial  
25 infarction and the like).

      The compound of the present invention and the pharmaceutical agent of the present invention is a glucose dependent insulin secretagogue that selectively promotes insulin secretion in hyperglycemic patients  
30 (e.g., patients showing fasting blood glucose level of not less than 126 mg/dl or 75 g oral glucose tolerance test (75 g OGTT) 2 h level of not less than 140 mg/dl and the like). Therefore, the compound of the present invention and the pharmaceutical agent of the present  
35 invention are useful as a safe prophylactic or therapeutic agent of diabetes with a low risk of

vascular complications, hypoglycemia induction and the like caused by insulin.

While the dose of the compound of the present invention and the pharmaceutical agent of the present invention varies depending on the administration subject, administration route, target disease, condition and the like, the compound of the present invention as an active ingredient is generally given in a single dose of about 0.01-100 mg/kg body weight, preferably 0.05-30 mg/kg body weight, more preferably 0.1-10 mg/kg body weight, in the case of, for example, oral administration to adult diabetic patients. This dose is desirably given 1 to 3 times a day.

The compound of the present invention can be used in combination with therapeutic agents such as a therapeutic agent of diabetes, a therapeutic agent of diabetic complications, an antihyperlipemia agent, an antihypertensive agent, an antiobestic agent, a diuretic, a chemotherapeutic agent, an immunotherapeutic agent, an antithrombotic agent, a therapeutic agent of osteoporosis, an antidementia agent, an agent for the improvement of erectile dysfunction, a therapeutic agent of incontinencia or pollakiuria and the like (hereinafter to be referred to as a combination drug). In this case, the timing of administration of the compound of the present invention and a combination drug is not limited. These may be simultaneously administered to an administration object or administered in a staggered manner. Moreover, the compound of the present invention and a combination drug may be administered as two kinds of preparations each containing an active ingredient, or may be administered as a single preparation containing both active ingredients.

The dose of the combination drug can be determined as appropriate based on the dose clinically employed.

The proportion of the compound of the present invention and combination drug can be appropriately determined depending on the administration subject, administration route, target disease, condition, combination and the like. When, for example, the administration subject is human, a combination drug is used in an amount of 0.01-100 parts by weight per 1 part by weight of the compound of the present invention.

Examples of the therapeutic agent of diabetes include insulin preparations (e.g., animal insulin preparations extracted from pancreas of cattle, swine; human insulin preparations synthesized by genetic engineering techniques using *Escherichia coli* or yeast; zinc insulin; protamine zinc insulin; fragments or derivatives of insulin (e.g., INS-1 and the like) and the like), insulin sensitizers (e.g., pioglitazone hydrochloride, rosiglitazone (maleate), GI-262570, JTT-501, MCC-555, YM-440, KRP-297, CS-011, FK-614, NN-622, AZ-242, BMS-298585, EML-16336, compounds described in WO99/58510 (e.g., (E)-4-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyloxyimino]-4-phenylbutyric acid) and the like), PPAR $\gamma$  agonists, PPAR $\gamma$  antagonists, PPAR $\gamma$ / $\alpha$  dual agonists,  $\alpha$ -glucosidase inhibitors (e.g., voglibose, acarbose, miglitol, emiglitate and the like), biguanides (e.g., phenformin, metformin, buformin and the like), insulin secretagogues [sulfonylureas (e.g., tolbutamide, glibenclamide, gliclazide, chlorpropamide, tolazamide, acetohexamide, glycopyramide, glimepiride, glipizide, glybuzole and the like), repaglinide, senaglinide, nateglinide, mitiglinide or calcium salt hydrate thereof], GLP-1 receptor agonists [e.g., GLP-1, NN-2211, AC-2993 (exendin-4), BIM-51077, Aib(8,35)hGLP-1(7,37)NH<sub>2</sub> and the like], amylin agonists (e.g., pramlintide and the like), phosphotyrosine phosphatase inhibitors (e.g., vanadic acid and the like), dipeptidylpeptidase IV inhibitors (e.g., NVP-DPP-278, PT-100, P32/98, LAF-237

and the like),  $\beta$ 3 agonists (e.g., CL-316243, SR-58611-A, UL-TG-307, SB-226552, AJ-9677, BMS-196085, AZ40140 and the like), gluconeogenesis inhibitors (e.g., glycogen phosphorylase inhibitors, glucose-6-phosphatase inhibitors, glucagon antagonists, somatostatin receptor agonists and the like), SGLT (sodium-glucose cotransporter) inhibitors (e.g., T-1095 and the like) and the like.

Examples of the therapeutic agent of diabetic complications include aldose reductase inhibitors (e.g., Tolrestat, Epalrestat, Zenarestat, Zopolrestat, Minalrestat, Fidarestat, SNK-860, CT-112 and the like), neurotrophic factors and increasing drugs thereof (e.g., NGF, NT-3, BDNF, neurotrophin production secretion promoters described in WO01/14372 (e.g., 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-[3-(2-methylphenoxy)propyl]oxazole and the like) and the like), neuranogenesis stimulators (e.g., Y-128 and the like), PKC inhibitors (e.g., LY-333531 and the like), AGE inhibitors (e.g., ALT946, pimagedine, pyratoxanthine, N-phenacylthiazolium bromide (ALT766), EXO-226 and the like), active oxygen scavengers (e.g., thiocetic acid and the like), cerebral vasodilators (e.g., tiapride, mexiletine and the like), and the like.

Examples of the antihyperlipemia agent include statin compounds which are cholesterol synthesis inhibitors (e.g., cerivastatin, pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin, itavastatin and salts thereof (e.g., sodium salt) and the like), squalene synthase inhibitors (e.g., compounds described in WO97/10224, such as N-[[[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzooxazepin-3-yl]acetyl]-piperidine-4-acetic acid and the like) or fibrate compounds having a triglyceride lowering action (e.g., bezafibrate, clofibrate, simfibrate, clinofibrate and

the like), ACAT inhibitors (e.g., Avasimibe, Eflucimibe and the like), anion exchange resins (e.g., colestyramine and the like), probucol, nicotinic acid drugs (e.g., nicomol, niceritrol and the like), ethyl  
5 icosapentate, plant sterols (e.g., soysterol,  $\gamma$ -oryzanol and the like) and the like.

Examples of the antihypertensive agent include angiotensin converting enzyme inhibitors (e.g., captopril, enalapril, delapril and the like) or  
10 angiotensin II antagonists (e.g., candesartan cilexetil, losartan, eprosartan, valsartan, telmisartan, irbesartan, tasosartan and the like), calcium antagonists (e.g., manidipine, nifedipine, amlodipine, efonidipine, nicardipine and the like), potassium channel openers  
15 (e.g., levcromakalim, L-27152, AL 0671, NIP-121 and the like), Clonidine and the like.

Examples of the antiobestic agent include central  
antiobestic agents (e.g., Dexfenfluramine, fenfluramine, phentermine, Sibutramine, amfepramone, dexamphetamine,  
20 Mazindol, phenylpropanolamine, clobenzorex and the like), pancreatic lipase inhibitors (e.g., orlistat and the like),  $\beta$ 3 agonists (e.g., CL-316243, SR-58611-A, UL-TG-307, SB-226552, AJ-9677, BMS-196085, AZ40140 and the like), peptide anorexiant (e.g., leptin, CNTF (Ciliary  
25 Neurotropic Factor) and the like), cholecystokinin agonists (e.g., lintitript, FPL-15849 and the like) and the like.

Examples of the diuretic include xanthine derivatives (e.g., sodium salicylate and theobromine,  
30 calcium salicylate and theobromine and the like), thiazide preparations (e.g., ethiazide, cyclopenthiazide, trichloromethiazide, hydrochlorothiazide, hydroflumethiazide, benzylhydrochlorothiazide, penflutizide, polythiazide, methyclothiazide and the  
35 like), antialdosterone agents (e.g., spironolactone, triamterene and the like), carbonate dehydrating enzyme



inhibitors (e.g., acetazolamide and the like),  
chlorobenzenesulfonamide agents (e.g., chlortalidone,  
mefruside, indapamide and the like), azosemide,  
isosorbide, etacrynic acid, piretanide, bumetanide,  
5 furosemide and the like.

Examples of the chemotherapeutic agent include  
alkylation agents (e.g., cyclophosphamide, ifosfamide  
and the like), metabolic antagonists (e.g., methotrexate,  
5-fluorouracil and the like), anti-cancer antibiotics  
10 (e.g., mitomycin, adriamycin and the like), plant-  
derived anti-cancer agents (e.g., vincristin, vindesine,  
taxol and the like), cisplatin, carboplatin, etoposide  
and the like. Of these, furtulon and neofurtulon which  
are 5-fluorouracil derivatives and the like are  
15 preferable.

Examples of the immunotherapeutic agent include  
microorganism or bacterial components (e.g., muramyl  
dipeptide derivative, picibanil and the like),  
polysaccharides having immunity potentiating activity  
20 (e.g., lentinan, sizofiran, krestin and the like),  
cytokines obtained by genetic engineering techniques  
(e.g., interferon, interleukin (IL) and the like),  
colony stimulating factors (e.g., granulocyte  
stimulating factor, erythropoietin and the like) and the  
25 like, with preference given to IL-1, IL-2, IL-12 and the  
like.

Examples of the antithrombotic agent include  
heparin (e.g., heparin sodium, heparin calcium,  
dalteparin sodium and the like), warfarin (e.g.,  
30 warfarin potassium and the like), anti-thrombin drugs  
(e.g., aragatroban and the like), thrombolytic agents  
(e.g., urokinase, tisokinase, alteplase, nateplase,  
monteplase, pamiteplase and the like), platelet  
aggregation inhibitors (e.g., ticlopidine hydrochloride,  
35 cilostazol, ethyl icosapentate, beraprost sodium,  
sarpogrelate hydrochloride and the like) and the like.

Examples of the therapeutic agent of osteoporosis include alfacalcidol, calcitriol, elcaltonin, calcitonin salmon, estriol, ipriflavone, pamidronate disodium, alendronate sodium hydrate, incadronate disodium and the  
5 like.

Examples of the antidementia agent include tacrine, donepezil, rivastigmine, galantamine and the like.

Examples of the agent for improving erectile dysfunction include apomorphine, sildenafil citrate and  
10 the like.

Examples of the therapeutic agent of incontinencia or pollakiuria include flavoxate hydrochloride, oxybutynin hydrochloride, propiverine hydrochloride and  
the like.

15 Furthermore, drugs having a cachexia-improving action established in animal models and clinical situations, such as cyclooxygenase inhibitors (e.g., Indometacin and the like) [Cancer Research, vol. 49, 5935-5939, 1989], Progesterone derivatives (e.g.,  
20 Megesterol acetate) [Journal of Clinical Oncology, vol. 12, 213-225, 1994], glucosteroid (e.g., dexamethasone and the like), metoclopramide agents, tetrahydrocannabinol agents (*ibid.*), fat metabolism improving agents (e.g., eicosapentaenoic acid and the  
25 like) [British Journal of Cancer, vol. 68, 314-318, 1993], growth hormones, IGF-1, or antibodies to a cachexia-induced factor such as TNF- $\alpha$ , LIF, IL-6, Oncostatin M and the like, can be used in combination with the compound of the present invention.

30 The combination drug is preferably an insulin preparation, an insulin sensitizer, an  $\alpha$ -glucosidase inhibitor, a biguanide, an insulin secretagogue (preferably a sulfonylurea) or the like.

Two or more of the above-mentioned combination  
35 drugs can be used in combination in an appropriate ratio. Preferable combinations in the case of using two or

more combination drugs are, for example, as shown in the following.

- 1) an insulin secretagogue (preferably a sulfonylurea) and an  $\alpha$ -glucosidase inhibitor;
- 5 2) an insulin secretagogue (preferably a sulfonylurea) and a biguanide;
- 3) an insulin secretagogue (preferably a sulfonylurea), a biguanide and an  $\alpha$ -glucosidase inhibitor;
- 4) an insulin sensitizer and an  $\alpha$ -glucosidase inhibitor;
- 10 5) an insulin sensitizer and a biguanide;
- 6) an insulin sensitizer, a biguanide and an  $\alpha$ -glucosidase inhibitor.

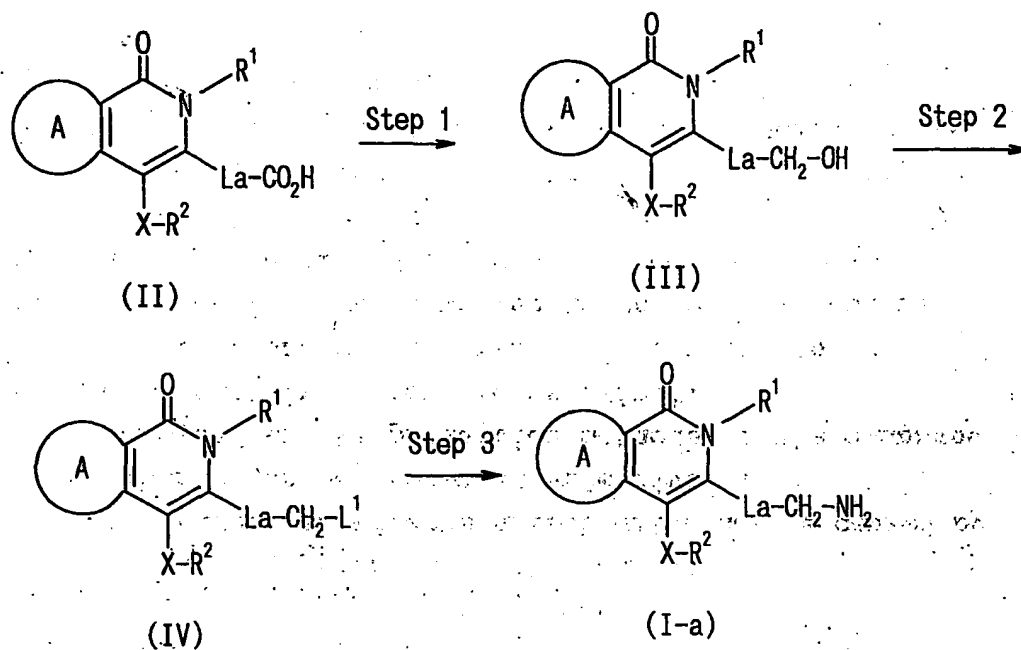
When the compound of the present invention or the pharmaceutical agent of the present invention is used in  
15 combination with a combination drug, the amount thereof can be reduced within a safe range in consideration of counteraction of these agents. Particularly, the dose of an insulin sensitizer, an insulin secretagogue (preferably a sulfonylurea) and a biguanide can be  
20 reduced as compared with the normal dose. Therefore, an adverse effect which may be caused by these agents can be prevented safely. In addition, the dose of the therapeutic agent of diabetic complications, antihyperlipemia agent and antihypertensive agent can be  
25 reduced whereby an adverse effect which may be caused by these agents can be prevented effectively.

Hereinafter the production methods of the compound of the present invention are explained.

The compound of the present invention can be  
30 produced according to a method known *per se*, such as a method to be described in detail in the following, or an analogous method thereto.

For example, compound (I-a) of the formula (I) wherein L is alkylene can be produced according to the  
35 following Method A or an analogous method thereto.

[Method A]



wherein  $La$  is a bond or alkylene,  $L^1$  is a leaving group,  
 5 and other symbols are as defined above.

The alkylene for  $La$  is exemplified by that mentioned as the aforementioned  $L$ . When  $L$  is alkylene,  $L$  is the same as  $La(CH_2)$ .

The leaving group for  $L^1$  may be, for example,  
 10 halogen atom (e.g., chlorine, bromine, iodine and the like), optionally halogenated  $C_{1-6}$  alkylsulfonyloxy (e.g., methanesulfonyloxy, ethanesulfonyloxy, trifluoromethanesulfonyloxy and the like), optionally substituted  $C_{6-10}$  arylsulfonyloxy, hydroxy and the like.

15 Examples of the substituent in the "optionally substituted  $C_{6-10}$  arylsulfonyloxy" include halogen atom (e.g., chlorine, bromine, iodine and the like), optionally halogenated  $C_{1-6}$  alkyl or  $C_{1-6}$  alkoxy and the like. The number of the substituent(s) is, for example,  
 20 1 to 3. Specific examples of the "optionally substituted  $C_{6-10}$  arylsulfonyloxy" include benzenesulfonyloxy, p-toluenesulfonyloxy, 1-

naphthalenesulfonyloxy, 2-naphthalenesulfonyloxy and the like.

The "leaving group" is preferably halogen atom (e.g., chlorine, bromine, iodine and the like),  
5 methanesulfonyloxy, trifluoromethanesulfonyloxy, p-toluenesulfonyloxy and the like.

(Step 1)

This reaction is carried out by directly reducing with a reducing agent (e.g., borane, lithium aluminum  
10 hydride and the like) in a solvent that does not adversely influence the reaction, or converting a carboxyl group to its reactive derivative (e.g., acid halide, mixed acid anhydride, active ester, ester and the like) and reducing with a reducing agent (e.g.,  
15 sodium borohydride, sodium lithium borohydride, lithium aluminum hydride, diisobutyl aluminum hydride and the like).

The amount of the reducing agent to be used is preferably from about 0.5 to about 10 molar equivalents  
20 per compound (II).

The solvent that does not adversely influence the reaction varies depending on the reducing agent. Examples thereof include aromatic hydrocarbons such as benzene, toluene, xylene and the like; halogenated  
25 hydrocarbons such as chloroform, dichloromethane and the like; ethers such as tetrahydrofuran, 1,2-dimethoxyethane, dioxane, diethyl ether and the like; water; alcohols such as methanol, ethanol, isopropanol and the like; and the like. Two or more of these  
30 solvents may be used upon mixing at a suitable ratio.

The reaction temperature is generally from about -50°C to about 150°C, preferably about -10°C to about 100°C.

The reaction time is generally from about 0.5 to  
35 about 20 hours.

The compound (III) thus obtained can be isolated

and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and  
5 the like.

(Step 2)

When  $L^1$  is a halogen atom, this reaction is carried out using a halogenating agent in a solvent that does not adversely influence the reaction.

10 Examples of the halogenating agent include thionyl chloride, phosphorus tribromide and the like.

The amount of the halogenating agent to be used is preferably 1 to about 20 molar equivalents per compound (III).

15 Examples of the solvent that does not adversely influence the reaction include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; halogenated hydrocarbons such as chloroform,  
20 dichloromethane and the like, and the like. Two or more of these solvents may be used upon mixing at a suitable ratio. It is also possible to use an excess halogenating agent as a solvent.

The reaction temperature is generally from about -  
25 20°C to about 150°C, preferably about 0°C to about 100°C.

The reaction time is generally from about 0.1 to about 20 hours.

When  $L^1$  is an optionally halogenated  $C_{1-6}$  alkylsulfonyloxy or an optionally substituted  $C_{6-10}$   
30 arylsulfonyloxy, this reaction is carried out using a sulfonylating agent in the presence of a base in a solvent that does not adversely influence the reaction.

Examples of the sulfonylating agent include mesyl chloride, tosyl chloride, benzenesulfonyl chloride and  
35 the like.

Examples of the base include amines such as

triethylamine, N-methylmorpholine, N,N-dimethylaniline and the like; alkali metal salts such as sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like; and the like.

5       The amount of the sulfonylating agent and the base to be used is preferably 1 to about 2 molar equivalents per compound (III).

      Examples of the solvent that does not adversely influence the reaction include aromatic hydrocarbons  
10 such as benzene, toluene, xylene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; ethyl acetate and the like.

      Two or more of these solvents may be used upon mixing  
15 at a suitable ratio.

      The reaction temperature is generally about -20°C to about 150°C, preferably about 0°C to about 100°C.

      The reaction time is generally from about 0.1 to about 20 hours.

20       The thus-obtained compound (IV) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and  
25 the like.

(Step 3)

      This reaction is carried out by reacting compound (IV) and an aminating agent in a solvent that does not adversely influence the reaction, and subjecting the  
30 obtained compound to deprotection of an amino group as necessary.

      Examples of the aminating agent include ammonia, hexamethylenetetramine, potassium phthalimide, di-t-butyl dicarboxylimide and the like.

35       The amount of the aminating agent to be used is preferably about 1 to about 5 molar equivalents per

compound (IV).

Examples of the solvent that does not adversely influence the reaction include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; alcohols such as methanol, ethanol, isopropanol and the like; ketones such as acetone, 2-butanone and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide and the like; and the like. Two or more of these solvents may be used upon mixing at a suitable ratio.

The reaction temperature is about 0°C to about 200°C, preferably about 20°C to about 120°C.

The reaction time is generally from about 0.5 to about 20 hours.

The amino group is deprotected according to a method known *per se*.

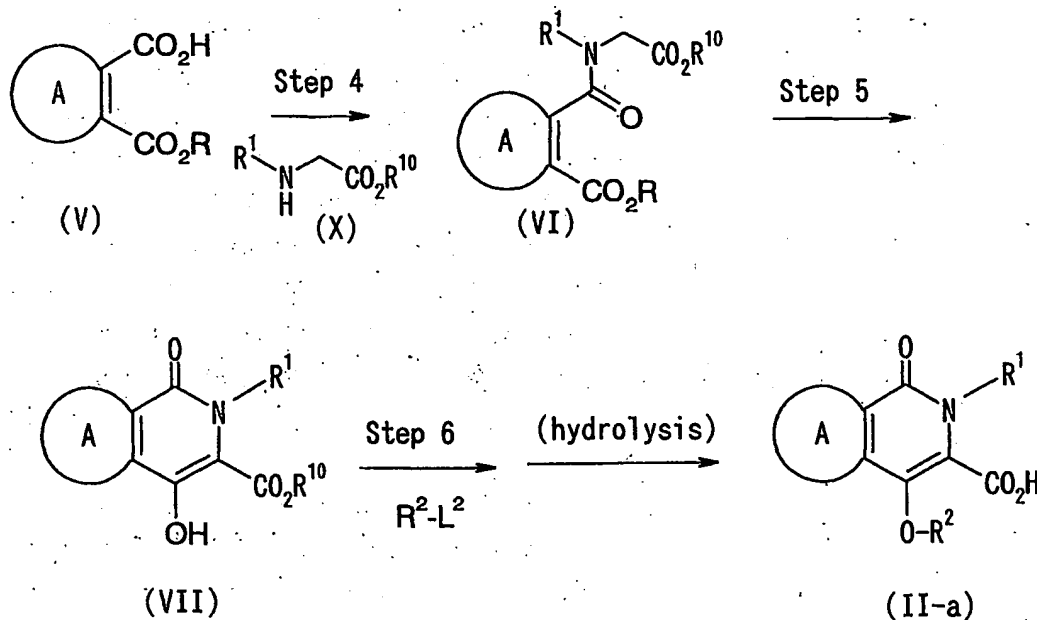
The thus-obtained compound (I-a) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

The compound (II) used as a starting material compound in Method A can be produced according to a method known *per se*, for example, the methods detailed in the following or analogous methods thereto.

The compound (II-a) which is a compound of the formula (II) wherein La is a bond and X is -O- can be produced according to the method described in, for example, Journal of Heterocyclic chemistry, vol. 7, 1057 (1970), the following Method B, or analogous methods thereto.

[Method B]





wherein R is a  $\text{C}_{1-6}$  alkyl group,  $\text{R}^{10}$  is a hydrogen atom or an optionally substituted hydrocarbon group,  $\text{L}^2$  is a leaving group and other symbols are as defined above.

Examples of the  $\text{C}_{1-6}$  alkyl group for R include methyl, ethyl and the like.

The "optionally substituted hydrocarbon group" for  $\text{R}^{10}$  is exemplified by that mentioned as the aforementioned  $\text{R}^3$ .

The leaving group for  $\text{L}^2$  is exemplified by that mentioned as the aforementioned  $\text{L}^1$ . The leaving group for  $\text{L}^2$  may be a hydroxy group.

#### 15 (Step 4)

This reaction is carried out according to, for example, a method comprising direct condensation of compound (V) and glycine derivative (X) using a condensation agent (e.g., dicyclohexylcarbodiimide and the like), or a method comprising appropriately reacting a reactive derivative of compound (V) and a glycine derivative and the like. Examples of the reactive

derivative include acid anhydride, acid halide (e.g., acid chloride, acid bromide), imidazolidine, or mixed acid anhydride (e.g., anhydride with methyl carbonate, ethyl carbonate or isobutyl carbonate and the like) and the like.

When, for example, acid halide is used as a reactive derivative of compound (V), the reaction is carried out in the presence of a base in a solvent that does not adversely influence the reaction.

Examples of the base include amines such as triethylamine, N-methylmorpholine, N,N-dimethylaniline and the like; alkali metal salts such as sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like; and the like.

Examples of the solvent that does not adversely influence the reaction include halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; ethyl acetate, water and the like. Two or more of these solvents may be used upon mixing at a suitable ratio.

The amount of the glycine derivative (X) to be used is 0.1 to 10 molar equivalents, preferably 1 to 3 molar equivalents, per compound (V).

The reaction temperature is about -30°C to about 100°C.

The reaction time is generally 0.5 to 20 hours.

When a mixed acid anhydride is used as a reactive derivative of compound (V), compound (V) and chlorocarbonate ester (e.g., methyl chlorocarbonate, ethyl chlorocarbonate, isobutyl chlorocarbonate and the like) are reacted in the presence of a base and then reacted with glycine derivative (X).

Examples of the base include amines such as triethylamine, N-methylmorpholine, N,N-dimethylaniline

and the like; alkali metal salts such as sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like; and the like.

The amount of the glycine derivative (X) to be used  
5 is generally 0.1 to 10 molar equivalents, preferably 0.3 to 3 molar equivalents, per compound (V).

The reaction temperature is generally from about - 30°C to about 100°C.

The reaction time is generally from 0.5 to 20 hours.

10 The thus-obtained compound (VI) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and  
15 the like.

The compound (V) and glycine derivative (X) used as a starting material compound in step 4 can be produced according to a method known per se.

(Step 5)

20 This reaction is carried out according to a conventional method in the presence of a base in a solvent that does not adversely influence the reaction.

Examples of the base include metalhydrides such as sodium hydride, potassium hydride and the like; alkali  
25 metal alkoxides such as sodium methoxide, sodium ethoxide, potassium t-butoxide and the like; alkali metal salts such as potassium hydroxide, sodium hydroxide, sodium hydrogencarbonate, potassium carbonate and the like; amines such as pyridine, triethylamine,  
30 N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undeca-7-ene and the like.

The amount of the base to be used is preferably about 0.1 to about 2 molar equivalents per compound (VI).

Examples of the solvent that does not adversely  
35 influence the reaction include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers

such as tetrahydrofuran, dioxane, diethyl ether and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; water; alcohols such as methanol, ethanol, isopropanol and the like; ketones  
5 such as acetone, 2-butanone and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide and the like; and the like. Two or more of these solvents may be used upon mixing at a suitable ratio.

10 The reaction temperature is about  $-10^{\circ}\text{C}$  to about  $150^{\circ}\text{C}$ , preferably about  $0^{\circ}\text{C}$  to about  $110^{\circ}\text{C}$ .

The reaction time is generally from about 0.5 to about 20 hours.

The thus-obtained compound (VII) can be isolated  
15 and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

20 (Step 6)

When  $\text{L}^2$  is a hydroxy group, this reaction is carried out by a method known *per se*, such as a method described in Synthesis, page 1 (1981), or an analogous method thereto.

25 This reaction is generally carried out in the presence of an organic phosphorus compound and electrophil in a solvent that does not adversely influence the reaction.

Examples of the organic phosphorus compound include  
30 triphenylphosphine, tributylphosphine and the like.

Examples of the electrophil include diethyl azodicarboxylate, diisopropyl azodicarboxylate, azodicarbonyldipiperazine and the like.

The amount of the organic phosphorus compound and  
35 electrophil to be used is preferably about 1 to about 5 molar equivalents per compound (VII).

Examples of the solvent that does not adversely influence the reaction include ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide and the like; and the like. Two or more of these solvents may be used upon mixing at a suitable ratio.

The reaction temperature is about -50°C to about 150°C, preferably about -10°C to about 100°C.

The reaction time is generally from about 0.5 to about 20 hours.

When  $L^2$  is a halogen atom, an optionally halogenated  $C_{1-6}$  alkylsulfonyloxy or an optionally substituted  $C_{6-10}$  arylsulfonyloxy, this reaction is carried out according to a conventional method in the presence of a base in a solvent that does not adversely influence the reaction.

Examples of the base include alkali metal salts such as potassium hydroxide, sodium hydroxide, sodium hydrogencarbonate, potassium carbonate and the like; amines such as pyridine, triethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undeca-7-ene and the like; metalhydrides such as potassium hydride, sodium hydride and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, potassium t-butoxide and the like; and the like.

The amount of the base to be used is preferably about 1 to about 5 molar equivalents per compound (VII).

Examples of the solvent that does not adversely influence the reaction include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; ketones such as acetone, 2-butanone and the like;

halogenated hydrocarbons such as chloroform, dichloromethane and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide and the like; and the like. Two or more of these solvents may be used upon mixing at a suitable ratio.

The reaction temperature is generally about  $-50^{\circ}\text{C}$  to about  $150^{\circ}\text{C}$ , preferably about  $-10^{\circ}\text{C}$  to about  $100^{\circ}\text{C}$ .

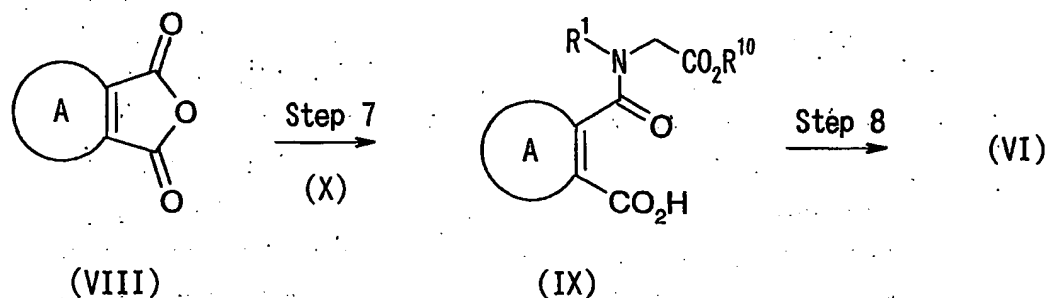
The reaction time is generally from about 0.5 to about 20 hours.

The compound obtained from the aforementioned step 6 is hydrolyzed, where necessary, by a method known per se to give compound (II-a).

The thus-obtained compound (II-a) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

The compound (VI) to be used in the aforementioned Method B can be also produced according to the following Method C.

[Method C]



wherein the symbols are as defined above.

(Step 7)

This reaction is carried out according to a conventional method in a solvent that does not adversely

influence the reaction.

Examples of the solvent that does not adversely influence the reaction include halogenated hydrocarbons such as chloroform, dichloromethane and the like;

5 aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; ethyl acetate and the like. Two or more of these solvents may be used upon mixing at a suitable ratio.

10 The amount of the glycine derivative (X) to be used is about 1 to about 10 molar equivalents, preferably 1 to 3 molar equivalents per compound (VIII).

The reaction temperature is generally from -30°C to 100°C.

15 The reaction time is generally from 0.5 to 20 hours.

The thus-obtained compound (IX) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced  
20 pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

The compound (VIII) used as a starting material compound in Step 7 can be produced according to a method  
25 known per se.  
(Step 8)

This reaction is carried out according to a conventional method in the presence of a base and a C<sub>1-6</sub> alkyl halide in a solvent that does not adversely  
30 influence the reaction.

Examples of the base include alkali metal salts such as potassium hydroxide, sodium hydroxide, sodium hydrogencarbonate, potassium carbonate and the like; amines such as pyridine, triethylamine, N,N-  
35 dimethylaniline, 1,8-diazabicyclo[5.4.0]undeca-7-ene and the like.

The amount of the base to be used is preferably about 1 to about 2 molar equivalents per compound (IX).

Examples of the C<sub>1-6</sub> alkyl halide include iodomethane, iodoethane and the like.

5 The amount of the C<sub>1-6</sub> alkyl halide to be used is preferably about 1 to about 2 molar equivalents per compound (IX).

Examples of the solvent that does not adversely influence the reaction include aromatic hydrocarbons  
10 such as benzene, toluene, xylene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; ketones such as acetone, 2-butanone and the like; amides such as N,N-  
15 dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide and the like; and the like. Two or more of these solvents may be used upon mixing at a suitable ratio.

The reaction temperature is generally from about -  
20 10°C to about 150°C, preferably 0°C to 110°C.

The reaction time is generally from about 0.5 to about 20 hours.

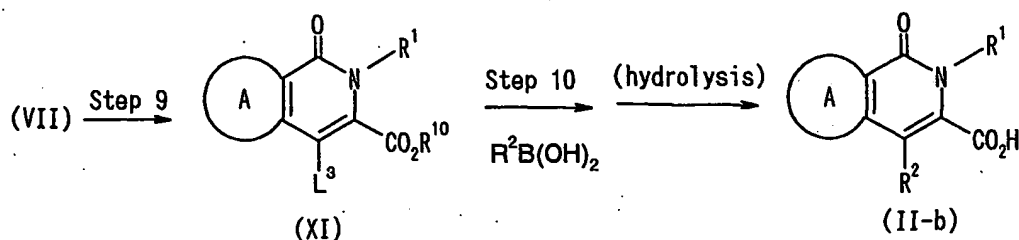
The thus-obtained compound (VI) can be isolated and purified by a known separation and purification means,  
25 such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

The compound (II-b) which is a compound of the  
30 formula (II) wherein La is a bond and X is a bond can be produced by a method described in, for example, JP-A-7-76573, JP-A-2000-72751 or JP-A-2000-72675, the following Method D or analogous methods thereto.

[Method D]

35





wherein  $L^3$  is a leaving group, and other symbols are as defined above.

5 The leaving group for  $L^3$  is exemplified by that mentioned as the aforementioned  $L^1$ .

(Step 9)

When, for example,  $L^3$  is an optionally halogenated  $C_{1-6}$  alkylsulfonyloxy or an optionally substituted  $C_{6-10}$  arylsulfonyloxy, this reaction is carried out according to a conventional method in the presence of a base and a sulfonylating agent in a solvent that does not adversely influence the reaction.

15 Examples of the base include metalhydrides such as sodium hydride, potassium hydride and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, potassium t-butoxide and the like; alkali metal salts such as potassium hydroxide, sodium hydroxide, sodium hydrogencarbonate, potassium carbonate and the like; amines such as pyridine, triethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undeca-7-ene and the like.

The amount of the base to be used is preferably about 1 to about 5 molar equivalents per compound (VII).

25 Examples of the sulfonylating agent include N-phenyltrifluoromethanesulfonimide, anhydrous trifluoromethanesulfonic acid and the like.

The amount of the sulfonylating agent to be used is preferably about 1 to about 5 molar equivalents per 30 compound (VII).

Examples of the solvent that does not adversely

influence the reaction include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; and the like. Two or more of these solvents may be used upon mixing at a suitable ratio.

The reaction temperature is generally from about -50°C to about 150°C, preferably about -10°C to about 20°C.

10 The reaction time is generally from about 0.5 to about 20 hours.

The thus-obtained compound (XI) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

(Step 10)

This reaction is carried out according to a conventional method in the presence of a base and a metal catalyst in a solvent that does not adversely influence the reaction under an inert gas atmosphere.

Examples of the base include metalhydrides such as sodium hydride, potassium hydride and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, potassium t-butoxide and the like; alkali metal salts such as potassium hydroxide, sodium hydroxide, sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like; amines such as pyridine, triethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undeca-7-ene and the like. Of these, alkali metal salts such as sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like are preferable.

35 The amount of the base to be used is preferably about 1 to about 5 molar equivalents per compound (XI).

Examples of the metal catalyst include palladium complex such as tetrakis(triphenylphosphine)palladium(0) and the like.

The amount of use of the metal catalyst is preferably about 0.01 to about 0.5 molar equivalents per compound (XI).

Examples of the solvent that does not adversely influence the reaction include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; water; alcohols such as methanol, ethanol, isopropanol and the like; ketones such as acetone, 2-butanone and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide and the like; and the like. Two or more of these solvents may be used upon mixing at a suitable ratio.

Examples of the inert gas include argon, nitrogen and the like.

The reaction temperature is generally from about -10°C to about 150°C; preferably about 0°C to about 100°C.

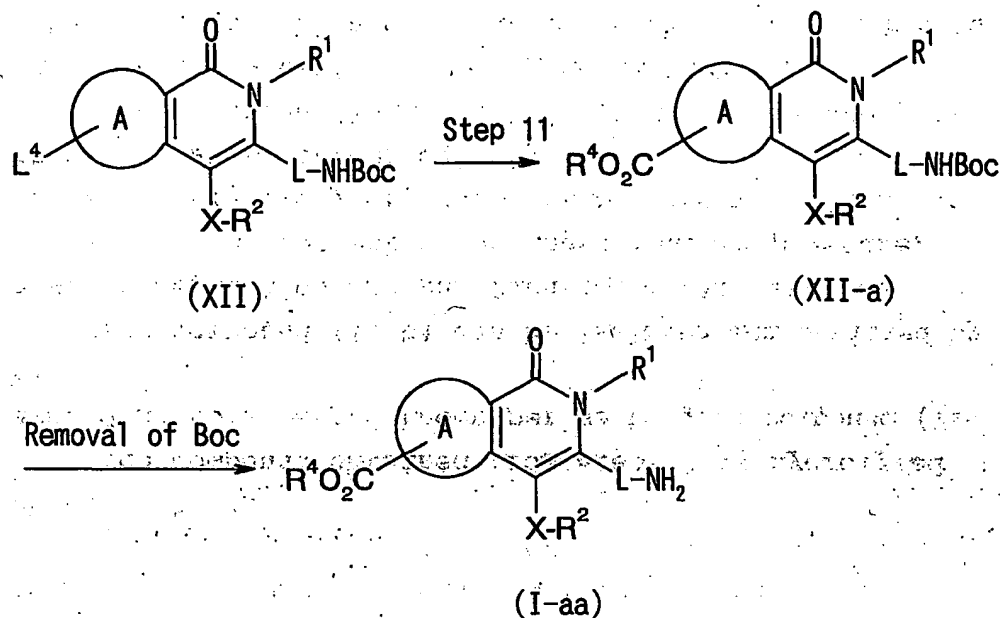
The reaction time is generally from about 0.5 to about 20 hours.

The compound obtained from Step 10 is hydrolyzed according to a method known per se to give compound (II-b).

The compound (II-b) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

The compound (I-aa) wherein ring A has a group of the formula:  $-\text{CO}-\text{OR}^4$  ( $\text{R}^4$  is as defined above) as a substituent can be also produced by the following Method E.

## [Method E]



5 wherein  $L^4$  is a leaving group, Boc is a t-butoxycarbonyl group and other symbols are as defined above.

The leaving group for  $L^4$  is exemplified by that mentioned as the aforementioned  $L^1$ .

## (Step 11)

10 This reaction is carried out in the presence of carbon monoxide, a metal catalyst, a reaction reagent and an alcohol in a solvent that does not adversely influence the reaction.

The metal catalyst is, for example, a palladium catalyst (e.g., palladium acetate and the like).

The amount of the metal catalyst to be used is preferably about 0.01 to about 1 molar equivalent per compound (XII).

20 The reaction reagent is, for example, an organic phosphorus compound (e.g., 1,3-bis(diphenylphosphino)propane and the like), a base (e.g., amines such as pyridine, triethylamine, N,N-

dimethylaniline etc., and the like), and the like.

The amount of the reaction reagent to be used is preferably about 1 to about 5 molar equivalents per compound (XII).

5 As the alcohol, an excess amount of ethanol or methanol is generally used.

Examples of the solvent that does not adversely influence the reaction include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers  
10 such as tetrahydrofuran, dioxane, diethyl ether and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide and the like; and the like. Two or  
15 more of these solvents may be used upon mixing at a suitable ratio.

The reaction temperature is generally from about 0°C to about 150°C, preferably about 50°C to about 100°C.

The reaction time is generally from about 0.5 to  
20 about 20 hours.

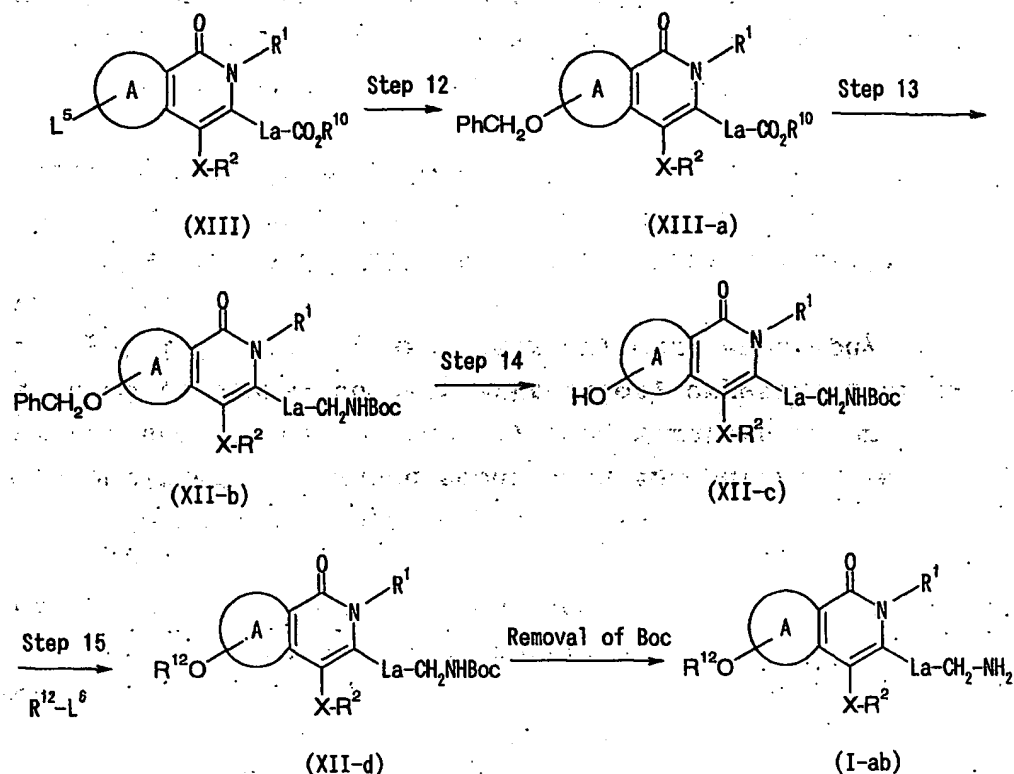
From compound (XII-a) obtained from Step 11, Boc group is removed by a method known per se to give compound (I-aa).

The thus-obtained compound (I-aa) can be isolated  
25 and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

30 The compound (XII) used as a starting material compound in Method E can be produced according to, for example, the aforementioned Method A or an analogous method thereto.

The compound (I-ab) wherein ring A has an  
35 optionally substituted hydroxy group as a substituent can be also produced by the following Method F.

## [Method F]



5 wherein  $L^5$  and  $L^6$  are leaving group,  $R^{12}$  is an optionally substituted hydrocarbon group and other symbols are as defined above.

The leaving group for  $L^5$  and  $L^6$  are exemplified by that mentioned as the aforementioned  $L^1$ .

10 Examples of the "optionally substituted hydrocarbon group" for  $R^{12}$  include each optionally substituted "alkyl group having 1 to 10 carbon atom(s)", "alkenyl group having 2 to 10 carbon atoms", "alkynyl group having 2 to 10 carbon atoms", "cycloalkyl group having 3 to 10 carbon atoms", "cycloalkenyl group having 3 to 10 carbon atoms", "aryl group having 6 to 14 carbon atoms" and "aralkyl having 7 to 13 carbon atoms" mentioned in the "optionally substituted hydroxy group" as the substituent in ring A.

**(Step 12)**

This reaction is carried out using benzyl alcohol in the presence of a base in a solvent that does not adversely influence the reaction.

5        Examples of the base include alkali metal salts such as potassium hydroxide, sodium hydroxide, sodium hydrogencarbonate, potassium carbonate and the like; amines such as pyridine, triethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undeca-7-ene and  
10 the like; metalhydrides such as potassium hydride, sodium hydride and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, potassium t.-butoxide and the like; and the like.

The amount of the base to be used is preferably  
15 about 1 to about 5 molar equivalents per compound (XIII).

The amount of benzyl alcohol to be used is preferably about 1 to about 3 molar equivalents per compound (XIII).

20        Examples of the solvent that does not adversely influence the reaction include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; amides such as N,N-  
25 dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide and the like; and the like. Two or more of these solvents may be used upon mixing at a suitable ratio.

The reaction temperature is generally from about  
30 0°C to about 150°C, preferably about 50°C to about 100°C.

The reaction time is generally from about 0.5 to about 20 hours.

The thus-obtained compound (XIII-a) can be isolated and purified by a known separation and purification  
35 means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization,

recrystallization, phase transfer, chromatography and the like.

(Step 13)

This reaction is carried out by introducing a Boc group according to a method known per se after reaction in the same manner as in the aforementioned Steps 1 to 3.

The thus-obtained compound (XII-b) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

(Step 14)

This reaction is carried out according to a per se known hydrogenation under a hydrogen atmosphere or in the presence of a hydrogen source such as formic acid and the like and a metal catalyst in a solvent that does not adversely influence the reaction.

Examples of the metal catalyst include a transition metal catalyst such as palladium-carbon, palladium black, platinum oxide, Raney-nickel, Wilkinson's catalyst etc., and the like.

The amount of the metal catalyst to be used is preferably about 0.01 to about 10 molar equivalents per compound (XII-b).

Examples of the solvent that does not adversely influence the reaction include lower organic acids such as acetic acid and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; amides such as N,N-dimethylformamide and the like; alcohols such as methanol, ethanol, isopropanol and the like; and the like. Two or more of these solvents may be used upon mixing at a suitable ratio.

The reaction temperature is generally from about 0°C to about 150°C, preferably about 0°C to about 100°C.

The reaction time is generally from about 0.5 to



about 20 hours.

The thus-obtained compound (XII-c) can be isolated and purified by a known separation and purification means, such as concentration, concentration under  
5 reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

(Step 15)

This Step is carried out by the reaction in the  
10 same manner as in the aforementioned Step 8.

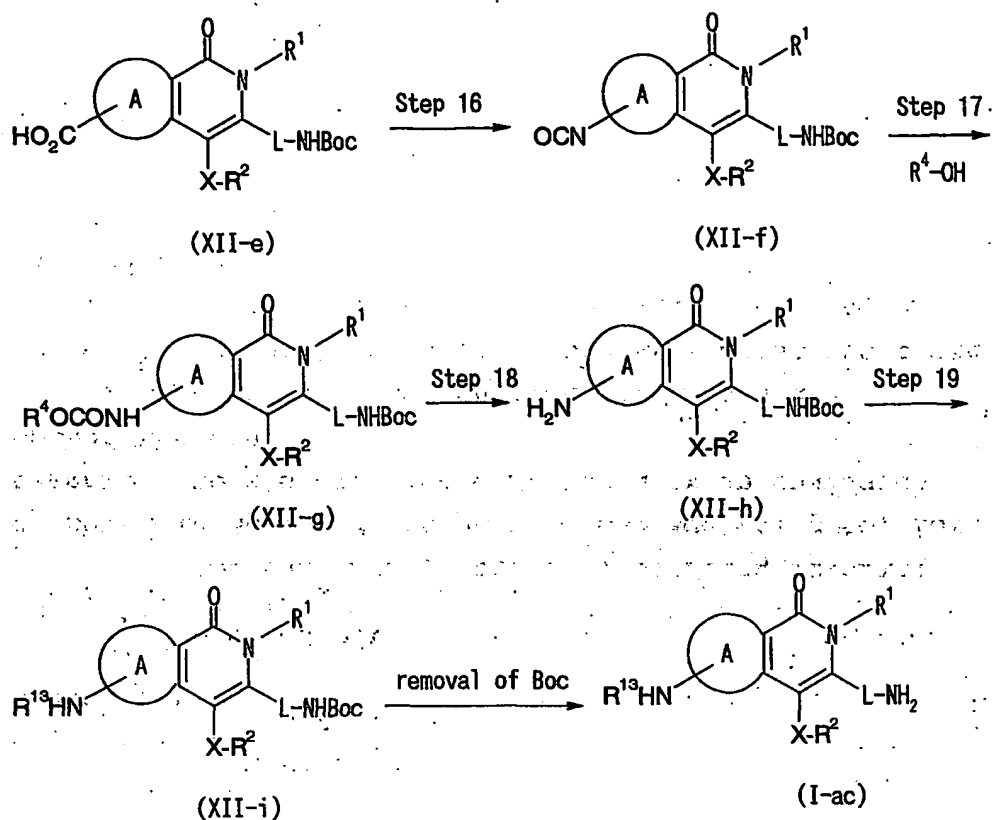
The thus-obtained compound (XII-d) can be isolated and purified by a known separation and purification means, such as concentration, concentration under  
15 reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

The compound (I-ab) can be produced by removing a Boc group from compound (XII-d) according to a method known per se.

20 The compound (I-ab) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

25 The compound (XIII) used as a starting material compound in Method F can be produced according to, for example, the aforementioned Method A or an analogous method thereto.

The compound (I-ac) wherein ring A has an  
30 optionally substituted amino group as a substituent can be also produced according to the following Method G.  
[Method G]



wherein  $R^{13}$  is a hydrocarbon group or an acyl group and other symbols are as defined above.

- 5        Examples of the "hydrocarbon group" for  $R^{13}$  include "alkyl group having 1 to 10 carbon atom(s)", "alkenyl group having 2 to 10 carbon atoms", "cycloalkyl group having 3 to 10 carbon atoms", "cycloalkenyl group having 3 to 10 carbon atoms" and "aryl group having 6 to 14
- 10 carbon atoms" mentioned in the "optionally substituted amino group" as the substituent in ring A. Examples of the acyl group for  $R^{13}$  is exemplified by that mentioned as the substituent in ring A.

**(Step 16)**

- 15        In this Step, compound (XII-e) and diphenylphosphoryl azide are reacted in the presence of a base in a solvent that does not adversely influence the reaction to give an acyl azide compound, which is

subjected to Curtius rearrangement reaction to give isocyanic acid derivative (XII-f).

The amount of the diphenylphosphoryl azide to be used is 1 to 10 molar equivalent(s), preferably 1.5 to 3 molar equivalents, per compound (XII-e).

Examples of the base include amines such as triethylamine, 4-dimethylaminopyridine, triethylenediamine, tetramethylethylenediamine and the like.

10 The amount of the base to be used is preferably about 1 to about 5 molar equivalents per compound (XII-e).

Examples of the solvent that does not adversely influence the reaction include ethers such as diethyl  
15 ether, tetrahydrofuran, dioxane and the like; halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform and the like; dimethylformamide and the like. Two or more of these solvents may be used upon mixing at a suitable ratio.

20 The reaction temperature is -20°C to 50°C, preferably 0°C to 20°C.

The reaction time is from 0.5 to 5 hours, preferably from 1 to 2 hours.

The Curtius rearrangement reaction is carried out  
25 according to a method known per se in a solvent that does not adversely influence the reaction.

Examples of the solvent that does not adversely influence the reaction include hydrocarbons such as benzene, toluene, xylene and the like; ethers such as  
30 diethyl ether, tetrahydrofuran, dioxane and the like; halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform and the like; amides such as dimethylformamide and the like; and the like. Two or more of these solvents may be used upon mixing at a  
35 suitable ratio.

The reaction temperature is generally from 50°C to

200°C, preferably 80°C to 150°C.

The reaction time is generally from 0.5 to 12 hours, preferably from 1 to 3 hours.

The thus-obtained compound (XII-f) can be isolated  
5 and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

10 (Step 17)

This reaction is carried out in a solvent that does not adversely influence the reaction.

The amount of a compound of the formula:  $R^4-OH$   
(wherein the symbols are as defined above) to be used is  
15 preferably about 1 to about 5 molar equivalents per compound (XII-f).

Examples of the solvent that does not adversely influence the reaction include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers  
20 such as tetrahydrofuran, dioxane, diethyl ether and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide and the like; and the like. Two or  
25 more of these solvents may be used upon mixing at a suitable ratio.

The reaction temperature is generally from about 0°C to about 150°C, preferably about 50°C to about 100°C.

The reaction time is generally from about 0.5 to  
30 about 20 hours.

This reaction may be carried out in the presence of a catalytic amount of N,N-dimethylaminopyridine and the like.

The thus-obtained compound (XII-g) can be isolated  
35 and purified by a known separation and purification means, such as concentration, concentration under

reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

By using a compound of the formula:  $\text{HNR}^{4a}\text{R}^{5a}$

5 (wherein the symbols are as defined above) instead of a compound of the above-mentioned formula:  $\text{R}^4\text{-OH}$  (wherein the symbols are as defined above), a compound (XII-g) wherein the substituent:  $\text{R}^4\text{CONH-}$  is replaced by  $\text{R}^{4a}\text{R}^{5a}\text{NCONH-}$  can be produced.

10 (Step 18)

This reaction is carried out by deprotection (e.g., catalytic reduction, piperidine treatment and the like) generally employed in peptide chemistry and the like.

The thus-obtained compound (XII-h) can be isolated  
15 and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

20 (Step 19)

This reaction is carried out according to a conventional method using an alkylation agent, an acylation agent and the like in the presence of a condensation agent or a base in a solvent that does not  
25 adversely influence the reaction.

The alkylation agent is exemplified by alkyl halides, alkylsulfonates and the like.

The amount of the alkylation agent to be used is preferably about 1 to about 5 molar equivalents per  
30 compound (XII-h).

The acylation agent is exemplified by carboxylic acid, sulfonic acid, phosphoric acid, carbonic acid or reactive derivatives thereof (e.g., acid halide, acid anhydride, mixed acid anhydride, active ester and the  
35 like), isocyanide, isothiocyanide and the like.

The amount of the acylating agent to be used is

preferably about 1 to about 5 molar equivalents per compound (XII-h).

The condensation agent is exemplified by dicyclohexylcarbodiimide, diethyl cyanophosphate, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide and the like.

The amount of the condensation agent to be used is preferably about 1 to about 5 molar equivalents per compound (XII-h).

Examples of the base include alkali metal salts such as potassium hydroxide, sodium hydroxide, sodium hydrogencarbonate, potassium carbonate and the like; amines such as pyridine, triethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undeca-7-ene and the like; metalhydrides such as potassium hydride, sodium hydride and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, potassium t-butoxide and the like; and the like.

The amount of the base to be used is preferably about 1 to about 5 molar equivalents per compound (XII-h).

Examples of the solvent that does not adversely influence the reaction include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; ketones such as acetone, 2-butanone and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide and the like; and the like. Two or more of these solvents may be used upon mixing at a suitable ratio.

The reaction temperature is generally from about -50°C to about 150°C, preferably about -10°C to about 100°C.

The reaction time is generally from about 0.5 to about 20 hours.

The thus-obtained compound (XII-i) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

By removing a Boc group from the thus-obtained compound (XII-i) according to a method known *per se*, compound (I-ac) can be produced.

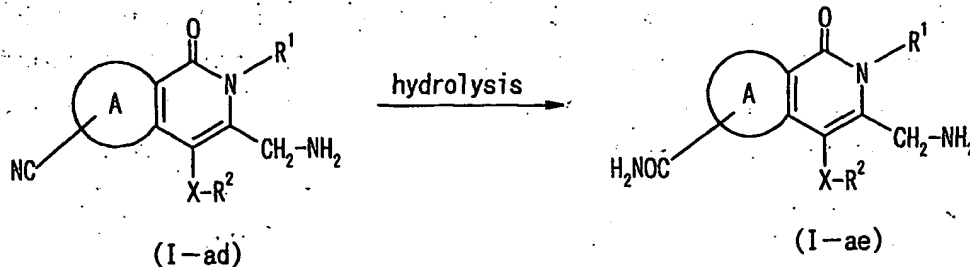
The compound (I-ac) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

Furthermore, by removing a Boc group from the aforementioned compound (XII-g) and compound (XII-h) according to a method known *per se*, a compound (I-ac) wherein the substituent:  $R^{13}HN-$  is respectively substituted by  $R^4OCONH-$  or amino can be produced.

The compound (XII-e) used as a starting material in Method G can be produced according to, for example, the aforementioned Method A, Method E or analogous methods thereto.

The compound (I-ae) which is a compound of the formula (I) wherein ring A has a carbamoyl group as a substituent and I is methylene can be also produced by, for example, the following Method H.

[Method H]



wherein the symbols are as defined above.

The hydrolysis can be generally carried out in the presence of an acid or a base.

5        Examples of the acid include mineral acids (e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and the like), carboxylic acids (e.g., formic acid, acetic acid, propionic acid and the like), and the like. Of these, hydrochloric acid, sulfuric  
10 acid and the like are preferable.

      Examples of the base include alkali metal salts such as lithium hydroxide, potassium hydroxide, sodium hydroxide, potassium carbonate, sodium carbonate, potassium hydrogencarbonate, sodium hydrogencarbonate  
15 and the like; alkaline earth metal salts such as calcium hydroxide, barium hydroxide and the like; amines such as trimethylamine, triethylamine, ethyldiisopropylamine, N-methylmorpholine and the like; and the like. Of these, potassium hydroxide, sodium hydroxide and the like are  
20 preferable.

      The amount of the acid or base to be used is, for example, 0.01 to 100 molar equivalents, preferably 0.1 to 50 molar equivalents per compound (I-ad).

      Hydrolysis is generally conducted in a solvent that  
25 does not adversely influence the reaction. Examples of the solvent include alcohols such as methanol, ethanol, propanol, 2-propanol, butanol, isobutanol, tert-butanol and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons  
30 such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butylmethyl ether, tetrahydrofuran, dioxane, dimethoxyethane and the like; amides such as dimethylformamide, dimethylacetamide and the like; sulfoxides such as dimethyl sulfoxide and the  
35 like; water and the like. Two or more of these solvents may be used upon mixing at a suitable ratio.



The reaction temperature is generally from 0°C to 150°C, preferably 10°C to 100°C.

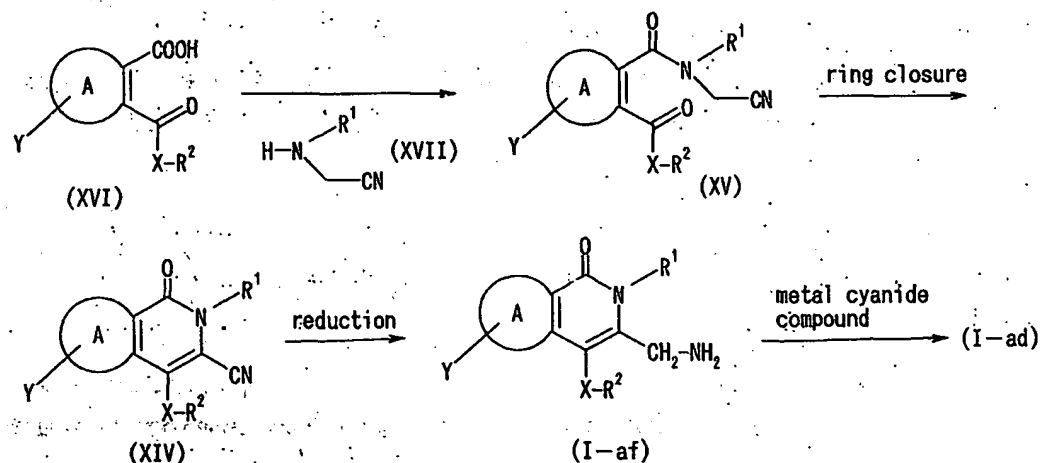
The reaction time is generally from 0.1 to about 100 hours, preferably from 0.1 to 10 hours.

5 The thus-obtained compound (I-ae) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and  
10 the like.

The compound (I-ad) used as a starting material compound in Method H can be produced according to, for example, the following Method I.

[Method I]

15



wherein the symbols are as defined above.

20 In this method, compound (XVI) and compound (XVII) are reacted to give compound (XV).

This reaction is carried out according to a per se known amidation reaction. This method may be, for example, a method comprising direct condensation of compound (XVI) and compound (XVII) using a condensation  
25 agent, a method comprising reacting a reactive derivative of compound (XVI) and compound (XVII), and

the like.

Examples of the condensation agent include carbodiimide condensation reagents such as dicyclohexylcarbodiimide, diisopropylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide and its hydrochloride, and the like; phosphoric acid condensation reagents such as diethyl cyanophosphate, diphenylphosphoryl azide and the like; carbonyldiimidazole, 2-chloro-1,3-dimethylimidazolium tetrafluoroborate and the like.

Examples of the solvent to be used for a reaction using a condensation agent include amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; sulfoxides such as dimethyl sulfoxide and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether, dimethoxyethane and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile, propionitrile and the like; water and the like. Two or more of these solvents may be used upon mixing at a suitable ratio.

The amount of the compound (XVII) to be used is generally 1 to 10 molar equivalents, preferably 1 to 3 molar equivalents, per compound (XVI).

The amount of the condensation agent to be used is generally 0.1 to 10 molar equivalents, preferably 0.3 to 3 molar equivalents, per compound (XVI).

When a carbodiimide condensation reagent is used as a condensation agent, the reaction efficiency can be increased by the use of a suitable condensation promoter (e.g., 1-hydroxy-7-azabenzotriazole, 1-hydroxybenzotriazole, N-hydroxysuccinimide, N-hydroxyphthalimide and the like) as necessary. When a phosphoric condensation reagent is used as a

condensation agent, the reaction efficiency can be increased by the use of an organic amine base such as triethylamine and the like.

The amount of the above-mentioned condensation promoter and organic amine base to be used is generally 0.1 to 10 molar equivalents, preferably 0.3 to 3 molar equivalents, per compound (XVI).

The reaction temperature is generally from -30°C to 120°C, preferably -10°C to 100°C.

The reaction time is generally from 0.5 to 60 hours.

The reactive derivative of compound (XVI) may be, for example, acid anhydride, acid halide (acid chloride, acid bromide), imidazolidine, mixed acid anhydride (e.g., anhydride with methylcarbonate, ethylcarbonate or isobutylcarbonate and the like) and the like.

When, for example, an acid anhydride or an acid halide is used, the reaction is generally carried out in the presence of a base in a solvent that does not adversely influence the reaction.

Examples of the base include amines such as triethylamine, pyridine, N-methylmorpholine, N,N-dimethylaniline, 4-dimethylaminopyridine and the like; alkali metal salts such as lithium hydroxide, sodium hydroxide, potassium hydroxide, sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like; and the like.

Examples of the solvent that does not adversely influence the reaction include amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; sulfoxides such as dimethyl sulfoxide and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether, dimethoxyethane and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles

such as acetonitrile, propionitrile and the like; water and the like. Two or more of these solvents may be used upon mixing at a suitable ratio.

When the above-mentioned amides are used as the  
5 solvent that does not adversely influence the reaction, the reaction may be carried out in the absence of a base.

The amount of the compound (XVII) to be used is generally 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents, per compound (XVI).

10 The amount of the base to be used is generally 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents per compound (XVI).

The reaction temperature is generally from -30°C to 100°C, preferably -10°C to 100°C.

15 The reaction time is generally from 0.5 to 30 hours.

When a mixed acid anhydride is used, compound (XVI) and chlorocarbonate (e.g., methyl chlorocarbonate, ethyl chlorocarbonate, isobutyl chlorocarbonate and the like) are reacted in the presence of a base, and the obtained  
20 compound is reacted with compound (XVII).

Examples of the base include amines such as triethylamine, aniline, N-methylmorpholine, N,N-dimethylaniline, 4-dimethylaminopyridine and the like; alkali metal salts such as sodium hydroxide, potassium  
25 hydroxide, lithium hydroxide, sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like; and the like.

The amount of the compound (XVII) to be used is generally 1 to 10 molar equivalents, preferably 1 to 5  
30 molar equivalents, per compound (XVI).

The amount of the base to be used is generally 1 to 10 molar equivalents, preferably 1 to 3 molar equivalents per compound (XVI).

The reaction temperature is generally from -30°C to  
35 120°C, preferably -10°C to 100°C.

The reaction time is generally from 0.5 to 20 hours.

The thus-obtained compound (XV) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, 5 recrystallization, phase transfer, chromatography and the like. It is also possible to subject a reaction mixture containing compound (XV) to the next reaction without isolating compound (XV).

The compound (XIV) is produced by subjecting the 10 compound (XV) to a ring closure reaction.

The ring closure reaction is generally carried out in the presence of a base in a solvent that does not adversely influence the reaction.

Examples of the base include amines such as 15 triethylamine, pyridine, N-methylmorpholine, N,N-dimethylaniline, 4-dimethylaminopyridine, 1,5-diazabicyclo[4.3.0]-5-nonene (DBN), 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) and the like; alkali metal salts such as lithium hydroxide, sodium 20 hydroxide, potassium hydroxide, sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like; and the like.

Examples of the solvent that does not adversely influence the reaction include amides such as N,N- 25 dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; sulfoxides such as dimethyl sulfoxide and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and 30 the like; ethers such as tetrahydrofuran, dioxane, diethyl ether, dimethoxyethane and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile, propionitrile and the like; water and the like. Two or more of these solvents may be used 35 upon mixing at a suitable ratio.

The amount of the base to be used is generally 0.01

to 10 molar equivalents, preferably 0.1 to 3 molar equivalents per compound (XV).

The reaction temperature is generally from -30°C to 120°C, preferably -10°C to 100°C.

5 The reaction time is generally from 0.5 to 40 hours.

The thus-obtained compound (XIV) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, 10 recrystallization, phase transfer, chromatography and the like. It is also possible to subject a reaction mixture containing compound (XIV) to the next reaction without isolating compound (XIV).

The compound (I-af) is produced by reducing 15 compound (XIV).

The reduction is performed according to a conventional method in the presence of a reducing agent in a solvent that does not adversely influence the reaction.

20 Examples of the reducing agent include metal hydrogen compounds such as bis(2-methoxyethoxy)aluminum sodium hydride, diisobutyl aluminum hydride and the like; metal hydrogen complex compounds such as sodium borohydride, sodium cyanide borohydride, aluminum 25 lithium hydride, aluminum sodium hydride and the like; and the like.

The amount of the reducing agent to be used is generally 0.1 to 20 molar equivalents per compound (XIV).

Examples of the solvent that does not adversely 30 influence the reaction include alcohols such as methanol, ethanol, propanol, 2-propanol, butanol, isobutanol, tert-butanol and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; 35 ethers such as diethyl ether, diisopropyl ether, tert-butylmethyl ether, tetrahydrofuran, dioxane,

dimethoxyethane and the like; esters such as methyl acetate, ethyl acetate, n-butyl acetate, tert-butyl acetate and the like; amides such as dimethylformamide, dimethylacetamide, N-methylpyrrolidone and the like.

5 Two or more of these solvents may be used upon mixing at a suitable ratio.

The reaction temperature is generally from -70°C to 150°C, preferably -20°C to 100°C.

10 The reaction time is generally from 0.1 to 100 hours, preferably from 0.1 to 40 hours.

The reduction reaction can be also conducted in the presence of a metal catalyst such as palladium-carbon, palladium black, palladium chloride, platinum oxide, platinum black, platinum-palladium, Raney-nickel, Raney-cobalt and the like, and a hydrogen source in a solvent  
15 that does not adversely influence the reaction.

The amount of the metal catalyst to be used is generally 0.001 to 1000 molar equivalents, preferably 0.01 to 100 molar equivalents, per compound (XIV).

20 Examples of the hydrogen source include hydrogen gas, formic acid, formic acid amine salt, phosphinate, hydrazine and the like.

The solvent that does not adversely influence the reaction is that employed for reduction using the  
25 aforementioned reducing agent.

The reaction temperature and reaction time are the same as those for reduction using the aforementioned reducing agent.

This reaction may be carried out in the presence of  
30 ammonia (e.g., aqueous ammonia, ammonia-ethanol and the like) as necessary. By reacting in the presence of ammonia, side reaction is suppressed and compound (I-af) can be produced in a high yield.

The thus-obtained compound (I-af) can be isolated  
35 and purified by a known separation and purification means, such as concentration, concentration under

reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like. It is also possible to subject a reaction mixture containing compound (I-af) to the next reaction  
5 without isolating compound (I-af).

The compound (I-ad) is produced by reacting compound (I-af) and a metal cyanide.

Examples of the metal cyanide include potassium cyanide, sodium cyanide, zinc cyanide and the like.

10 The reaction is generally carried out in a solvent that does not adversely influence the reaction.

Examples of the solvent that does not adversely influence the reaction include amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; sulfoxides such as  
15 dimethyl sulfoxide and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane,  
20 diethyl ether, dimethoxyethane and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile, propionitrile and the like; water and the like. Two or more of these solvents may be used upon mixing at a suitable ratio.

25 In this reaction, a catalyst may be used where necessary. Examples of the catalyst include transition metal compounds, such as rhodium, palladium-carbon, tetrakis(triphenylphosphine)palladium, tetrakis(tri-(2-toryl)phosphine)palladium, tetrakis(tri-(2-furyl)phosphine)palladium, bis(acetylacetonate)nickel,  
30 dichlorobis(triphenylphosphine)nickel, bis(1,5-cyclooctadiene)nickel, bis(1,10-phenanthroline)nickel, Raney-nickel, Raney-cobalt and the like.

The amount of the metal cyanide to be used is  
35 generally 1 to 100 molar equivalents, preferably 1 to 10 molar equivalents, per compound (I-af).



The amount of the catalyst to be used is generally 0.00001 to 10 molar equivalents, preferably 0.001 to 1 molar equivalent, per compound (I-af).

The reaction temperature is generally from -10°C to 250°C, preferably 0°C to 150°C.

The reaction time is generally from 0.1 to 100 hours, preferably 0.1 to 40 hours.

The thus-obtained compound (I-ad) can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

The compound (XVI) used as a starting material compound in Method I can be produced according to a method known *per se*.

In each of the aforementioned reactions, when the starting material compound has amino, carboxy, hydroxy or carbonyl as a substituent, a protecting group generally known in peptide chemistry and the like may be introduced into these groups. By removing the protecting group as necessary after the reaction, the objective compound can be obtained.

The amino-protecting group includes, for example, formyl, C<sub>1-6</sub> alkyl-carbonyl (e.g., acetyl, propionyl and the like), C<sub>1-6</sub> alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl and the like), benzoyl, C<sub>7-13</sub> aralkyl-carbonyl (e.g., benzylcarbonyl and the like), C<sub>7-13</sub> aralkyloxy-carbonyl (e.g., benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl and the like), trityl, phthaloyl, N,N-dimethylaminomethylene, silyl (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl and the like), C<sub>2-6</sub> alkenyl (e.g., 1-allyl and the like) and the like. These groups are optionally substituted by 1 to 3 halogen atom(s) (e.g.,

fluorine, chlorine, bromine, iodine and the like), C<sub>1-6</sub> alkoxy (e.g., methoxy, ethoxy, propoxy and the like) or nitro and the like.

The carboxy-protecting group is, for example, C<sub>1-6</sub> alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl and the like), C<sub>7-13</sub> aralkyl (e.g., benzyl and the like), phenyl, trityl, silyl (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl and the like), C<sub>2-6</sub> alkenyl (e.g., 1-allyl and the like) and the like. These groups are optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine and the like), C<sub>1-6</sub> alkoxy (e.g., methoxy, ethoxy, propoxy and the like) or nitro and the like.

The hydroxy-protecting group is, for example, C<sub>1-6</sub> alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl and the like), phenyl, trityl, C<sub>7-13</sub> aralkyl (e.g., benzyl and the like), formyl, C<sub>1-6</sub> alkyl-carbonyl (e.g., acetyl, propionyl and the like), benzoyl, C<sub>7-13</sub> aralkyl-carbonyl (e.g., benzylcarbonyl and the like), 2-tetrahydropyranyl, 2-tetrahydrofuranyl, silyl (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl and the like), C<sub>2-6</sub> alkenyl (e.g., 1-allyl and the like) and the like. These groups are optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine and the like), C<sub>1-6</sub> alkyl (e.g., methyl, ethyl, propyl and the like), C<sub>1-6</sub> alkoxy (e.g., methoxy, ethoxy, propoxy and the like) or nitro and the like.

The carbonyl-protecting group is, for example, cyclic acetal (e.g., 1,3-dioxane and the like), non-cyclic acetal (e.g., di-C<sub>1-6</sub> alkyl acetal and the like) and the like.

Introduction and removal of these protecting groups can follow a method known per se, for example, a method described in Protective Groups in Organic Synthesis,

John Wiley and Sons (1980) and the like. For example, employed is a method using acid, base, UV light, hydrazine, phenyl hydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride, 5 palladium acetate, trialkylsilyl halide (e.g., trimethylsilyl iodide, trimethylsilyl bromide and the like) and the like, reduction and the like.

When the starting material compound can form a salt in each of the aforementioned reactions, the compound in 10 the form of a salt may be used. The salt is, for example, the salt of compound (I) exemplified above.

When compound (I) contains an optical isomer, a stereoisomer, a positional isomer or a rotational isomer, these are also encompassed in compound (I), and can be 15 obtained as a single product according to a synthetic method and separation method known *per se*. For example, when compound (I) contains an optical isomer, an optical isomer resolved from this compound is also encompassed in compound (I).

20 The optical isomer can be produced by a method known *per se*. To be specific, an optically active synthetic intermediate is used, or the final racemate product is subjected to optical resolution according to a conventional method to give an optical isomer.

25 The method of optical resolution may be a method known *per se*, such as a fractional recrystallization method, a chiral column method, a diastereomer method and the like.

#### 1) Fractional recrystallization method

30 A salt of a racemate with an optically active compound (e.g., (+)-mandelic acid, (-)-mandelic acid, (+)-tartaric acid, (-)-tartaric acid, (+)-1-phenethylamine, (-)-1-phenethylamine, cinchonine, (-)-cinchonidine, brucine and the like) is formed, which is 35 separated by a fractional recrystallization method, and a free optical isomer is obtained by a neutralization

step where desired.

## 2) Chiral column method

A racemate or a salt thereof is applied to a column for separation of an optical isomer (chiral column) to  
5 allow separation. In the case of a liquid chromatography, for example, a mixture of an optical isomer is applied to a chiral column such as ENANTIO-OVM (manufactured by Tosoh Corporation) or CHIRAL series (manufactured by Daicel Chemical Industries, Ltd.) and  
10 the like, and developed with water, various buffers (e.g., phosphate buffer) and organic solvents (e.g., ethanol, methanol, isopropanol, acetonitrile, trifluoroacetic acid, diethylamine and the like) solely or in admixture to separate the optical isomer. In the  
15 case of a gas chromatography, for example, a chiral column such as CP-Chirasil-Dex CB (manufactured by GL Sciences Inc.) and the like is used to allow separation.

## 3) Diastereomer method

A racemate mixture is prepared into a diastereomer  
20 mixture by chemical reaction with an optically active reagent, which is prepared into a homogeneous substance by a typical separation means (e.g., fractional recrystallization, chromatography method and the like) and the like, and subjected to a chemical treatment such  
25 as hydrolysis and the like to separate the optically active reagent moiety, whereby an optical isomer is obtained. For example, when compound (I) contains hydroxy or primary or secondary amino in a molecule, the compound and an optically active organic acid (e.g.,  
30 MTPA [ $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetic acid], (-)-menthoxyacetic acid and the like) and the like are subjected to condensation to give an ester form or amide form diastereomer. When compound (I) has a carboxylic acid group, this compound and an optically active amine  
35 or an alcohol reagent are subjected to condensation to give an ester form or amide form diastereomer. The

separated diastereomer is converted to an optical isomer of the original compound by acid hydrolysis or base hydrolysis.

The compound (I) and a salt thereof may be in the  
5 form of a crystal.

The crystal of compound (I) or a salt thereof (hereinafter sometimes to be referred to as crystal of the present invention) can be produced by crystallization of compound (I) or a salt thereof by a  
10 crystallization method known per se.

Examples of the crystallization method include crystallization from a solution, crystallization from vapor, crystallization from a molten form and the like.

The "crystallization method from a solution" is  
15 typically a method including shifting a non-saturation state to hyper-saturation state by varying factors involved in solubility of compounds (solvent composition, pH, temperature, ionic strength, oxidation-reduction state and the like) or the amount of solvent. To be  
20 specific, for example, concentration method, annealing method, reaction method (diffusion method, electrolysis method), hydrothermal growth method, fusing agent method and the like can be mentioned. Examples of the solvent to be used include aromatic hydrocarbons (e.g., benzene,  
25 toluene, xylene and the like), halogenated hydrocarbons (e.g., dichloromethane, chloroform and the like), saturated hydrocarbons (e.g., hexane, heptane, cyclohexane and the like), ethers (e.g., diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane and the  
30 like), nitriles (e.g., acetonitrile and the like), ketones (e.g., acetone and the like), sulfoxides (e.g., dimethyl sulfoxide and the like), acid amides (e.g., N,N-dimethylformamide and the like), esters (e.g., ethyl acetate and the like), alcohols (e.g., methanol, ethanol,  
35 isopropyl alcohol and the like), water and the like. These solvents are used alone or in combination of two

or more at a suitable ratio (e.g., 1:1 to 1:100 (volume ratio)).

The "crystallization method from vapor" is, for example, vaporization method (sealed tube method, gas stream method), gas phase reaction method, chemical transportation method and the like.

The "crystallization method from a molten form" is, for example, normal freezing method (Czockralski method, temperature gradient method, Bridgman method), zone melting method (zone leveling method, floating zone method), special growth method (VLS method, liquid phase epitaxy method) and the like.

Preferable examples of the crystallization method include a method including dissolving compound (I) or a salt thereof in a suitable solvent (e.g., alcohols such as methanol, ethanol etc., and the like) at a temperature of 20-120°C and cooling the resulting solution to a temperature not higher than the temperature of dissolution (e.g., 0-50°C, preferably 0-20°C) and the like.

The thus-obtained crystals of the present invention can be isolated by, for example, filtration and the like.

In the present specification, the melting point refers to that measured using, for example, micromelting point measuring apparatus (Yanako, MP-500D) or DSC (differential scanning calorimetry) device (SEIKO, EXSTAR6000) and the like.

In the present specification, moreover, a peak by powder X-ray diffraction refers to that measured using, for example, RINT2100 (Rigaku Industrial Corporation) and the like using Cu-K $\alpha$ 1 ray (tube voltage: 40 KV; tube current: 50 mA) as a ray source.

In general, melting points and peaks by powder X-ray diffraction vary depending on measurement apparatuses, measurement conditions and the like. The crystal in the present specification may show a

different melting point or a peak by powder X-ray diffraction described in the present specification, as long as it is within general error range.

The crystal of the present invention is superior in  
5 physicochemical properties (e.g., melting point, solubility, stability and the like) and biological properties (e.g., pharmacokinetics (absorption, distribution, metabolism, excretion), efficacy expression and the like), and is extremely useful as a  
10 pharmaceutical agent.

The present invention is explained in more detail by the following Examples, Reference Examples, Experimental Examples and Formulation Examples. These  
do not limit the present invention and the present  
15 invention can be modified within the range that does not deviate from the scope of the invention.

The abbreviations in Examples and Reference Examples mean the following.

s: singlet, d: doublet, t: triplet, q: quartet, dd:  
20 double doublet, dt: double triplet, m: multiplet, bs: broad singlet, tt: triple triplet, J: coupling constant, room temperature: 0-30°C

#### Examples

##### Example 1

25 3-(Aminomethyl)-4-butoxy-6-ethoxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride

(1) A solution of 4-fluorophthalic anhydride (8.31 g, 50 mmol) and ethyl 2-(neopentylamino)acetate (10.40 g, 60 mmol) in tetrahydrofuran (50 ml) was stirred at room  
30 temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in N,N-  
35 dimethylformamide (50 ml), and potassium carbonate (6.91 g, 50 mmol) and ethyl iodide (4.8 ml, 60 mmol) were

added. The mixture was stirred at room temperature for 3 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in ethanol (50 ml) and 20% sodium ethoxide ethanol solution (34.04 g, 100 mmol) was added. The mixture was stirred at room temperature for 1 h. The reaction mixture was poured into 1N hydrochloric acid (150 ml) and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography and the component eluted earlier was concentrated to give ethyl 7-fluoro-4-hydroxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (5.12 g, 31.9%) as crystals.

Melting point 92-93°C.

Elemental analysis for  $C_{17}H_{20}NO_4F$ .

Calculated: C, 63.54; H, 6.27; N, 4.36.

Found: C, 63.56; H, 6.19; N, 4.16.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.85 (9H, s), 1.47 (3H, t,  $J=7.1$  Hz), 4.48 (2H, q,  $J=7.1$  Hz), 4.54 (2H, bs), 7.42-7.52 (1H, m), 8.10 (1H, dd,  $J=2.7, 9.2$  Hz), 8.17 (1H, dd,  $J=5.5, 9.2$  Hz), 10.19 (1H, s).

The component eluted later was concentrated to give ethyl 6-fluoro-4-hydroxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (3.85 g, 24.0%) as crystals.

Melting point 115-115.5°C.

Elemental analysis for  $C_{17}H_{20}NO_4F$ .

Calculated: C, 63.54; H, 6.27; N, 4.36.

Found: C, 63.54; H, 6.19; N, 4.11.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.85 (9H, s), 1.47 (3H, t,  $J=7.2$  Hz), 4.49 (2H, q,  $J=7.2$  Hz), 4.54 (2H, bs), 7.32-7.42 (1H, m), 7.72 (1H, dd,  $J=2.9, 9.2$  Hz), 8.47 (1H, dd,  $J=5.5, 9.2$  Hz), 10.70 (1H, s).



- (2) To a solution of ethyl 6-fluoro-4-hydroxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (3.21 g, 10 mmol), 1-butanol (1.4 ml, 15 mmol) and tributylphosphine (5.0 ml, 20 mmol) in tetrahydrofuran (30 ml) was added 1,1'-azodicarbonylpiperidine (5.05 g, 20 mmol) and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to give ethyl 4-butoxy-6-fluoro-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (3.55 g, 94.2%) as an oil.
- <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.94 (9H, s), 1.01 (3H, t, J=7.4 Hz), 1.44 (3H, t, J=7.1 Hz), 1.48-1.59 (2H, m), 1.73-1.89 (2H, m), 3.94 (2H, t, J=6.5 Hz), 4.07 (2H, bs), 4.44 (2H, q, J=7.1 Hz), 7.21-7.31 (1H, m), 7.38 (1H, dd, J=2.5, 9.1 Hz), 8.45 (1H, dd, J=5.6, 8.8 Hz).
- (3) To a solution of ethyl 4-butoxy-6-fluoro-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (3.40 g, 9 mmol) in tetrahydrofuran (20 ml) and ethanol (20 ml) was added sodium hydroxide (1.08 g, 27 mmol). The obtained mixture was refluxed under heating for 12 h. The reaction mixture was poured into water and acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 ml) and oxalyl chloride (0.9 ml, 10.8 mmol) and N,N-dimethylformamide (2 drops) were added thereto. The mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 ml). The obtained solution was added dropwise to a suspension of sodium tetrahydroborate (1.13 g, 30 mmol) in 1,2-dimethoxyethane (20 ml) at 0°C. The obtained mixture was stirred at 0°C for 1 h. The reaction mixture was poured

into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica  
5 gel column chromatography and the component eluted earlier was concentrated to give 4-butoxy-6-fluoro-3-hydroxymethyl-2-neopentyl-1(2H)-isoquinolinone (1.72 g, 57.1%) as crystals.

Melting point 143-143.5°C.

10 Elemental analysis for  $C_{19}H_{26}NO_3F$

Calculated: C, 68.04; H, 7.81; N, 4.18.

Found: C, 67.85; H, 7.72; N, 4.20.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.96 (9H, s), 1.00 (3H, t,  $J=7.3$  Hz),  
1.50-1.68 (2H, m), 1.79-1.93 (2H, m), 2.46 (1H, bs),  
15 3.88 (2H, t,  $J=6.6$  Hz), 4.17 (2H, bs), 4.87 (2H, bs),  
7.08-7.18 (1H, m), 7.24-7.30 (1H, m), 8.28-8.37 (1H, m).

The component eluted later was concentrated to give 4-butoxy-6-ethoxy-3-hydroxymethyl-2-neopentyl-1(2H)-isoquinolinone (0.51 g, 15.7%) as crystals.

20 Melting point 92.5-93.0°C.

Elemental analysis for  $C_{21}H_{31}NO_4$

Calculated: C, 69.78; H, 8.64; N, 3.87.

Found: C, 69.84; H, 8.65; N, 3.68.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.95 (9H, s), 1.03 (3H, t,  $J=7.3$  Hz),  
25 1.48 (3H, t,  $J=7.0$  Hz), 1.54-1.66 (2H, m), 1.79-1.89 (2H, m),  
2.77 (1H, bs), 3.89 (2H, t,  $J=6.4$  Hz), 4.13 (2H, q,  $J=7.0$  Hz),  
4.18 (2H, bs), 4.85 (2H, bs), 6.93-6.98 (2H, m), 8.17-8.22 (1H, m).

(4) To a solution of 4-butoxy-6-ethoxy-3-hydroxymethyl-2-neopentyl-1(2H)-isoquinolinone (0.43 g, 1.2 mmol) in  
30 tetrahydrofuran (10 ml) and toluene (10 ml) was added thionyl chloride (0.18 ml, 2.4 mmol). The obtained mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous  
35 sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried

over anhydrous magnesium sulfate and concentrated under reduced pressure to give 4-butoxy-6-ethoxy-3-chloromethyl-2-neopentyl-1(2H)-isoquinolinone (0.41 g, 91.1%) as an oil.

<sup>5</sup> <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.98 (9H, s), 1.04 (3H, t, J=7.3 Hz), 1.48 (3H, t, J=7.0 Hz), 1.55-1.70 (2H, m), 1.81-1.91 (2H, m), 3.95 (2H, t, J=6.5 Hz), 4.10 (2H, bs), 4.15 (2H, q, J=7.0 Hz), 4.87 (2H, bs), 7.05-7.30 (2H, m), 8.34 (1H, d, J=9.4 Hz).

<sup>10</sup> (5) A solution of 4-butoxy-6-ethoxy-3-chloromethyl-2-neopentyl-1(2H)-isoquinolinone (0.38 g, 1 mmol) and potassium phthalimide (0.28 g, 1.5 mmol) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 6 h. The reaction mixture was poured  
<sup>15</sup> into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 2-((4-butoxy-6-ethoxy-  
<sup>20</sup> 2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-dione (0.48 g, 98.0%) as an amorphous.

Elemental analysis for C<sub>29</sub>H<sub>34</sub>N<sub>2</sub>O<sub>5</sub>

Calculated: C, 71.00; H, 6.99; N, 5.71.

<sup>25</sup> Found: C, 71.41; H, 7.15; N, 5.64.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:1.00 (9H, s), 1.01 (3H, t, J=7.3 Hz), 1.48 (3H, t, J=7.0 Hz), 1.50-1.61 (2H, m), 1.81-1.94 (2H, m), 3.99 (2H, bs), 4.02 (2H, t, J=6.8 Hz), 4.15 (2H, q, J=7.0 Hz), 5.07 (2H, s), 7.02-7.10 (2H, m), 7.69-7.80  
<sup>30</sup> (1H, m), 8.31 (1H, d, J=8.8 Hz).

(6) To a solution of 2-((4-butoxy-6-ethoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-dione (0.43 g, 1.2 mmol) in ethanol (20 ml) was added hydrazine monohydrate (0.13 ml, 2.7 mmol). The  
<sup>35</sup> obtained mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous

- sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in
- 5 tetrahydrofuran (20 ml) and di-*t*-butyl dicarbonate (0.31 g, 1.4 mmol) was added thereto. The obtained mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over
- 10 anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give *tert*-butyl (4-butoxy-6-ethoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl carbamate (0.36 g, 87.8%) as
- 15 crystals. Melting point 138-139°C. Elemental analysis for  $C_{26}H_{40}N_2O_5$  Calculated: C, 67.80; H, 8.75; N, 6.08. Found: C, 67.76; H, 8.91; N, 5.87.
- 20  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (9H, s), 1.03 (3H, t,  $J=7.0$  Hz), 1.45 (9H, s), 1.49 (3H, t,  $J=7.0$  Hz), 1.52-1.64 (2H, m), 1.79-1.91 (2H, m), 3.96 (2H, t,  $J=6.4$  Hz), 4.10 (2H, bs), 4.15 (2H, q,  $J=7.0$  Hz), 4.55 (2H, d,  $J=5.6$  Hz), 4.67 (1H, bs), 7.02-7.08 (2H, m), 8.29-8.34 (1H, m).
- 25 (7) To a solution of *tert*-butyl (4-butoxy-6-ethoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.28 g, 0.6 mmol) in ethyl acetate (5 ml) was added a solution of 4N hydrogen chloride in ethyl acetate (5 ml), and the obtained
- 30 solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol-diisopropyl ether to give 3-(aminomethyl)-4-butoxy-6-ethoxy-2-neopentyl-1(2H)-isoquinolinone
- 35 hydrochloride (0.23 g, 95.8%) as crystals. Melting point 195.5-201°C.

Elemental analysis for  $C_{21}H_{33}N_2O_3Cl \cdot 1/4H_2O$

Calculated: C, 62.83; H, 8.41; N, 6.98.

Found: C, 62.79; H, 8.52; N, 6.72.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.90 (9H, s), 1.00 (3H, t,  $J=7.3$  Hz),  
5 1.41 (3H, t,  $J=7.0$  Hz), 1.51-1.63 (2H, m), 1.77-1.91 (2H,  
m), 3.93 (2H, t,  $J=6.4$  Hz), 4.09 (2H, bs), 4.20 (2H, q,  
 $J=7.0$  Hz), 4.22 (2H, s), 7.07 (1H, d,  $J=2.2$  Hz), 7.18  
(1H, dd,  $J=2.2, 8.8$  Hz), 8.18 (1H, d,  $J=8.8$  Hz), 8.56  
(3H, bs).

10 **Example 2**

3-(Aminomethyl)-4-butoxy-7-fluoro-2-neopentyl-1(2H)-  
isoquinolinone hydrochloride

(1) To a solution of ethyl 7-fluoro-4-hydroxy-2-  
neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate  
15 (5.12 g, 31.9%) (from Example 1(1), 3.21 g, 10 mmol), 1-  
butanol (1.4 ml, 15 mmol) and tributylphosphine (5.0 ml,  
20 mmol) in tetrahydrofuran (30 ml) was added 1,1'-  
(azodicarbonyl)dipiperidine (5.05 g, 20 mmol) and the  
mixture was stirred at room temperature for 3 h. The  
20 reaction mixture was concentrated under reduced pressure  
and the residue was purified by silica gel column  
chromatography to give ethyl 4-butoxy-7-fluoro-2-  
neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate  
(3.55 g, 94.2%) as an oil.

25  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.94 (9H, s), 1.01 (3H, t,  $J=7.1$  Hz),  
1.44 (3H, t,  $J=7.1$  Hz), 1.51-1.63 (2H, m), 1.73-1.87 (2H,  
m), 3.95 (2H, t,  $J=6.4$  Hz), 4.11 (2H, bs), 4.43 (2H, q,  
 $J=7.1$  Hz), 7.40-7.50 (1H, m), 7.79 (1H, dd,  $J=5.2, 8.8$   
Hz), 8.09 (1H, dd,  $J=2.8, 9.4$  Hz).

30 (2) To a solution of 4-butoxy-7-fluoro-2-neopentyl-1-  
oxo-1,2-dihydro-3-isoquinolinecarboxylate (3.40 g, 9  
mmol) in tetrahydrofuran (20 ml) and ethanol (20 ml) was  
added sodium hydroxide (1.08 g, 27 mmol). The obtained  
mixture was refluxed under heating for 3 h. The  
35 reaction mixture was poured into water, and, after  
making the mixture acidic with 1N hydrochloric acid,

extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran-diisopropyl ether to give 4-butoxy-7-fluoro-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (3.04 g, 96.8%) as crystals.

Melting point 184-185°C.

Elemental analysis for  $C_{19}H_{24}NO_4F$

10 Calculated: C, 65.31; H, 6.92; N, 4.01.

Found: C, 65.49; H, 7.11; N, 3.77.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.94 (9H, s), 0.99 (3H, t,  $J=7.5$  Hz), 1.45-1.64 (2H, m), 1.77-1.91 (2H, m), 4.03 (2H, t,  $J=6.6$  Hz), 4.30 (2H, bs), 5.67 (1H, bs), 7.42-7.52 (1H, m), 7.80 (1H, dd,  $J=5.2, 8.8$  Hz), 8.09 (1H, dd,  $J=2.6, 9.2$  Hz).

(3) 4-Butoxy-7-fluoro-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (2.97 g, 8.5 mmol) was dissolved in tetrahydrofuran (30 ml) and oxalyl chloride (0.9 ml, 10.2 mmol) and N,N-dimethylformamide (2 drops) were added thereto. The mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in tetrahydrofuran (20 ml). The obtained solution was added dropwise to sodium tetrahydroborate (1.13 g, 30 mmol) in dimethoxyethane (20 ml) at 0°C. The obtained mixture was stirred at 0°C for 1 h. The reaction mixture was poured into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran-diisopropyl ether to give 4-butoxy-7-fluoro-3-hydroxymethyl-2-neopentyl-1(2H)-isoquinolinone (2.52 g, 88.4%) as crystals.

Melting point 149-150°C.

Elemental analysis for  $C_{19}H_{26}NO_3F$

Calculated: C, 68.04; H, 7.81; N, 4.18.

Found: C, 67.80; H, 8.00; N, 4.19.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.95 (9H, s), 1.04 (3H, t,  $J=7.1$  Hz),

5 1.50-1.69 (2H, m), 1.71-1.94 (2H, m), 2.93 (1H, bs),  
3.91 (2H, t,  $J=6.6$  Hz), 4.21 (2H, bs), 4.87 (2H, bs),  
7.27-7.36 (1H, m), 7.65 (1H, dd,  $J=5.0, 8.8$  Hz), 7.86  
(1H, dd,  $J=2.4, 9.2$  Hz).

(4) To a solution of 4-butoxy-7-fluoro-3-hydroxymethyl-  
10 2-neopentyl-1(2H)-isoquinolinone (2.35 g, 7 mmol) in  
tetrahydrofuran (10 ml) and toluene (10 ml) was added  
thionyl chloride (1.0 ml, 14 mmol) and the obtained  
mixture was refluxed under heating for 2 h. The  
reaction mixture was poured into saturated aqueous  
15 sodium hydrogencarbonate solution and extracted with  
ethyl acetate. The extract was washed with brine, dried  
over anhydrous magnesium sulfate and concentrated under  
reduced pressure to give 4-butoxy-7-fluoro-3-  
chloromethyl-2-neopentyl-1(2H)-isoquinolinone (2.04 g,  
20 82.6%) as an oil.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (9H, s), 1.04 (3H, t,  $J=7.3$  Hz),  
1.51-1.69 (2H, m), 1.81-1.91 (2H, m), 3.94 (2H, t,  $J=6.4$   
Hz), 4.20 (2H, bs), 4.88 (2H, bs), 7.38-7.48 (1H, m),  
7.75 (1H, dd,  $J=5.0, 8.8$  Hz), 8.09 (1H, dd,  $J=2.6, 9.0$   
25 Hz).

(5) A solution of 4-butoxy-7-fluoro-3-chloromethyl-2-  
neopentyl-1(2H)-isoquinolinone (1.95 g, 5.5 mmol) and  
potassium phthalimide (1.54 g, 8.3 mmol) in  $N,N$ -  
dimethylformamide (20 ml) was stirred at room  
30 temperature for 6 h. The reaction mixture was poured  
into water and extracted with ethyl acetate. After  
washing the extract with water, the extract was dried  
over anhydrous magnesium sulfate and concentrated under  
reduced pressure. The obtained crystals were  
35 recrystallized from ethyl acetate-diisopropyl ether to  
give 2-((4-butoxy-7-fluoro-2-neopentyl-1-oxo-1,2-

dihydro-3-isoquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione (2.46 g, 96.5%) as crystals.

Melting point 155-156°C.

Elemental analysis for  $C_{27}H_{29}N_2O_4F$

5 Calculated: C, 69.81; H, 6.29; N, 6.03.

Found: C, 69.84; H, 6.17; N, 5.88.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.00 (3H, t,  $J=7.3$  Hz), 1.01 (9H, s), 1.45-1.62 (2H, m), 1.81-1.95 (2H, m), 4.02 (2H, t,  $J=6.7$  Hz), 4.13 (2H, bs), 5.07 (2H, bs), 7.36-7.45 (1H, m), 7.69-7.83 (5H, m), 8.05 (1H, dd,  $J=2.6, 9.4$  Hz).

10 (6) To a suspension of 2-((4-butoxy-7-fluoro-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-dione (2.32 g, 5 mmol) in ethanol (20 ml) was added hydrazine monohydrate (0.73 ml, 15 mmol).  
15 The obtained mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under  
20 reduced pressure. The residue was dissolved in tetrahydrofuran (20 ml) and di-*t*-butyl dicarbonate (1.64 g, 7.5 mmol) was added thereto. The obtained mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl  
25 acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give *tert*-butyl (4-butoxy-7-fluoro-2-neopentyl-1-oxo-  
30 1,2-dihydro-3-isoquinolinyl)methylcarbamate (1.93 g, 88.9%) as crystals.

Melting point 149-150°C.

Elemental analysis for  $C_{24}H_{35}N_2O_4F$

Calculated: C, 66.34; H, 8.12; N, 6.45.

35 Found: C, 66.33; H, 8.14; N, 6.33.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (9H, s), 1.03 (3H, t,  $J=7.4$  Hz),



1.45 (9H, s), 1.52-1.67 (2H, m), 1.79-1.93 (2H, m), 3.86 (2H, t, J=6.4 Hz), 4.13 (2H, bs), 4.57 (2H, d, J=5.6 Hz), 4.68 (1H, bs), 7.36-7.45 (1H, m), 7.70 (1H, dd, J=5.1, 8.7 Hz), 8.05 (1H, dd, J=2.7, 9.3 Hz).

- 5 (7) To a solution of tert-butyl (4-butoxy-7-fluoro-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (1.74 g, 4 mmol) in ethyl acetate (5 ml) was added a solution of 4N hydrogen chloride in ethyl acetate (5 ml), and the obtained  
10 solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure and the precipitated crystals were recrystallized from methanol - diisopropyl ether to give 3-(aminomethyl)-4-butoxy-7-fluoro-2-neopentyl-1(2H)-isoquinolinone  
15 hydrochloride (1.42 g, 95.9%) as crystals. Melting point 198-199°C.

Elemental analysis for  $C_{19}H_{28}N_2O_2ClF \cdot 1/2H_2O$

Calculated: C, 60.07; H, 7.69; N, 7.37.

Found: C, 60.33; H, 7.57; N, 7.42.

- 20  $^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.91 (9H, s), 0.99 (3H, t, J=7.4 Hz), 1.45-1.64 (2H, m), 1.78-1.92 (2H, m), 3.94 (2H, t, J=6.4 Hz), 4.12 (2H, bs), 4.25 (2H, bs), 7.70-7.80 (1H, m), 7.87 (1H, dd, J=5.4, 9.0 Hz), 7.95 (1H, dd, J=2.5, 9.5 Hz), 8.60 (3H, bs).

25 **Example 3**

3-(Aminomethyl)-4-butoxy-6-fluoro-2-neopentyl-1(2H)-isoquinolinone hydrochloride

- (1) To a solution of 4-butoxy-6-fluoro-3-hydroxymethyl-2-neopentyl-1(2H)-isoquinolinone (from Example 1(3),  
30 1.68 g, 5 mmol) in tetrahydrofuran (10 ml) and toluene (10 ml) was added thionyl chloride (0.73 ml, 10 mmol), and the resulting mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted  
35 with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated

under reduced pressure to give 4-butoxy-6-fluoro-3-chloromethyl-2-neopentyl-1(2H)-isoquinolinone (1.62 g, 92.0%) as an oil.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.98 (9H, s), 1.04 (3H, t, J=7.4 Hz), 1.51-1.69 (2H, m), 1.81-1.95 (2H, m), 3.94 (2H, t, J=6.6 Hz), 4.17 (2H, bs), 4.87 (2H, bs), 7.12-7.30 (1H, m), 7.35 (1H, dd, J=2.6, 9.6 Hz), 8.09 (1H, dd, J=5.8, 9.0 Hz).

(2) A solution of 4-butoxy-6-fluoro-3-chloromethyl-2-neopentyl-1(2H)-isoquinolinone (1.59 g, 4.5 mmol) and potassium phthalimide (1.26 g, 6.8 mmol) in N,N-dimethylformamide (20 ml) was stirred at room temperature for 6 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give 2-((4-butoxy-6-fluoro-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-dione (1.81 g, 86.6%) as crystals.

Melting point 162-164°C.

Elemental analysis for C<sub>27</sub>H<sub>29</sub>N<sub>2</sub>O<sub>4</sub>F

Calculated: C, 69.81; H, 6.29; N, 6.03.

Found: C, 69.47; H, 6.10; N, 6.02.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:1.00 (9H, s), 1.01 (3H, t, J=7.3 Hz), 1.48-1.62 (2H, m), 1.81-1.95 (2H, m), 4.01 (2H, t, J=6.8 Hz), 4.04 (2H, bs), 5.07 (2H, bs), 7.13-7.23 (1H, m), 7.34 (1H, dd, J=2.4, 9.8 Hz), 7.70-7.86 (4H, m), 8.42 (1H, dd, J=5.6, 8.8 Hz).

(3) To a suspension of 2-((4-butoxy-6-fluoro-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-dione (1.71 g, 3.7 mmol) in ethanol (20 ml) was added hydrazine monohydrate (0.54 ml, 11.1 mmol). The resulting mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated

aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in  
5 tetrahydrofuran (20 ml) and di-*t*-butyl dicarbonate (1.22 g, 5.6 mmol) was added thereto. The obtained mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over  
10 anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting crystals were recrystallized from ethyl acetate - *n*-hexane to give *tert*-butyl (4-butoxy-6-fluoro-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (1.35 g, 83.9%)  
15 as crystals.

Melting point 168-169°C.

Elemental analysis for  $C_{24}H_{35}N_2O_4F$

Calculated: C, 66.34; H, 8.12; N, 6.45.

Found: C, 66.18; H, 8.26; N, 6.34.

20  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.00 (9H, s), 1.04 (3H, t,  $J=7.0$  Hz), 1.45 (9H, s), 1.52-1.67 (2H, m), 1.79-1.93 (2H, m), 3.85 (2H, t,  $J=6.4$  Hz), 4.11 (2H, bs), 4.56 (2H, d,  $J=5.2$  Hz), 4.68 (1H, bs), 7.14-7.24 (1H, m), 7.30 (1H, dd,  $J=2.6$ , 10.0 Hz), 8.42 (1H, dd,  $J=5.4$ , 8.8 Hz).

25 (4) To a solution of *tert*-butyl (4-butoxy-6-fluoro-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (1.22 g, 2.8 mmol) in ethyl acetate (5 ml) was added a solution of 4N hydrogen chloride in ethyl acetate (5 ml), and the obtained  
30 solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol-diisopropyl ether to give 3-(aminomethyl)-4-butoxy-6-fluoro-2-neopentyl-1(2H)-isoquinoline  
35 hydrochloride (1.01 g, 98.1%) as crystals.  
Melting point 195.5-201°C.

Elemental analysis for  $C_{19}H_{28}N_2O_2ClF \cdot 1/4H_2O$

Calculated: C, 62.83; H, 8.41; N, 6.98.

Found: C, 62.79; H, 8.52; N, 6.72.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.90 (9H, s), 1.00 (3H, t,  $J=7.3$  Hz),  
5 1.41 (3H, t,  $J=7.0$  Hz), 1.51-1.63 (2H, m), 1.77-1.91 (2H,  
m), 3.93 (2H, t,  $J=6.4$  Hz), 4.09 (2H, bs), 4.20 (2H, q,  
 $J=7.0$  Hz), 4.22 (2H, s), 7.07 (1H, d,  $J=2.2$  Hz), 7.18  
(1H, dd,  $J=2.2, 8.8$  Hz), 8.18 (1H, d,  $J=8.8$  Hz), 8.56  
(3H, bs).

10 **Example 4**

3-(Aminomethyl)-6-chloro-4-methoxy-2-methyl-1(2H)-  
isoquinolinone hydrochloride

(1) To a solution of 4-chlorophthalic anhydride (9.13 g,  
50 mmol) in tetrahydrofuran (50 ml) was added 28% sodium  
15 methoxide-methanol solution (11.6 ml, 60 mmol), and the  
mixture was stirred at room temperature for 30 min. The  
reaction mixture was poured into water, and, after  
making the mixture acidic with 1N hydrochloric acid,  
extracted with ethyl acetate. The extract was washed  
20 with brine, dried over anhydrous magnesium sulfate and  
concentrated under reduced pressure. The residue was  
dissolved in tetrahydrofuran (100 ml) and oxalyl  
chloride (5.2 ml, 60 mmol) and N,N-dimethylformamide (3  
drops) were added thereto. The mixture was stirred at  
25 room temperature for 30 min. The reaction mixture was  
concentrated under reduced pressure, and the residue was  
dissolved in N,N-dimethylacetamide (100 ml). To the  
obtained solution was added ethyl sarcosinate  
hydrochloride (9.22 g, 60 mmol). The obtained mixture  
30 was stirred at room temperature for 2 h. The reaction  
mixture was poured into 1N hydrochloric acid and  
extracted with ethyl acetate. The extract was washed  
with brine, dried over anhydrous magnesium sulfate and  
concentrated under reduced pressure. The residue was  
35 dissolved in ethanol (100 ml) and 20% sodium ethoxide  
ethanol solution (27.2 g, 80 mmol) was added. The

mixture was stirred at room temperature for 1 h. The reaction mixture was poured into 1N hydrochloric acid (100 ml) and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography and the component eluted earlier was concentrated to give ethyl 7-chloro-4-hydroxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (2.24 g, 20.9%) as crystals.

Melting point 109-110°C.

Elemental analysis for  $C_{13}H_{12}NO_4Cl$

Calculated: C, 55.43; H, 4.29; N, 4.97.

Found: C, 55.54; H, 4.22; N, 5.12.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.46 (3H, t,  $J=7.0$  Hz), 3.68 (3H, s), 4.50 (2H, q,  $J=7.0$  Hz), 7.70 (1H, dd,  $J=2.0, 8.6$  Hz), 8.09 (1H, d,  $J=8.6$  Hz), 8.43 (1H, d,  $J=2.0$  Hz), 11.25 (1H, s).

The component eluted later was concentrated to give ethyl 6-chloro-4-hydroxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (2.82 g, 26.4%) as crystals.

Melting point 110-111°C.

Elemental analysis for  $C_{13}H_{12}NO_4Cl$

Calculated: C, 55.43; H, 4.29; N, 4.97.

Found: C, 55.49; H, 4.30; N, 5.11.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.46 (3H, t,  $J=7.0$  Hz), 3.68 (3H, s), 4.50 (2H, q,  $J=7.0$  Hz), 7.63 (1H, dd,  $J=1.9, 8.7$  Hz), 8.17 (1H, d,  $J=1.9$  Hz), 8.38 (1H, d,  $J=8.7$  Hz), 11.16 (1H, s).

(2) A suspension of ethyl 6-chloro-4-hydroxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (1.41 g, 5 mmol), methyl iodide (0.47 ml, 7.5 mmol) and potassium carbonate (1.04 g, 7.5 mmol) in *N,N*-dimethylformamide (10 ml) was stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column

chromatography to give ethyl 6-chloro-4-methoxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (1.11 g, 75.5%) as crystals.

Melting point 122-123°C.

5 Elemental analysis for  $C_{14}H_{14}NO_4Cl$

Calculated: C, 56.86; H, 4.77; N, 4.74.

Found: C, 56.85; H, 4.76; N, 4.57.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.45 (3H, t,  $J=7.2$  Hz), 3.52 (3H, s),  
3.89 (3H, s), 4.49 (2H, q,  $J=7.2$  Hz), 7.51 (1H, dd,  
10  $J=2.2$ , 8.8 Hz), 7.74 (1H, d,  $J=2.2$  Hz), 8.38 (1H, d,  
 $J=8.8$  Hz).

(3) To a solution of ethyl 6-chloro-4-methoxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (1.03 g, 3.5 mmol) in tetrahydrofuran (10 ml) and ethanol (10 ml) was  
15 added 1N sodium hydroxide (5 ml). The obtained mixture was refluxed under stirring at 50°C for 3 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous  
20 magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diethyl ether to give 6-chloro-4-methoxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (0.72 g, 77.4%) as crystals.

25 Melting point 216-217°C.

Elemental analysis for  $C_{12}H_{10}NO_4Cl$

Calculated: C, 53.85; H, 3.77; N, 5.23.

Found: C, 53.78; H, 3.74; N, 5.03.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 3.58 (3H, s), 3.91 (3H, s), 4.78 (1H, bs),  
30 7.49 (1H, dd,  $J=2.0$ , 8.6 Hz), 7.75 (1H, d,  $J=2.0$  Hz),  
8.36 (1H, d,  $J=8.6$  Hz).

(4) 6-Chloro-4-methoxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (0.67 g, 2.5 mmol) was dissolved in tetrahydrofuran (10 ml) and oxalyl chloride  
35 (0.26 ml, 3 mmol) and  $N,N$ -dimethylformamide (2 drops) were added thereto. The mixture was stirred at room

- temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (10 ml). The obtained solution was added dropwise to a suspension of sodium
- 5 tetrahydroborate (0.33 g, 8.8 mmol) in 1,2-dimethoxyethane (20 ml) at 0°C. The obtained mixture was stirred at 0°C for 1 h, and the reaction mixture was poured into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried
- 10 over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate-diisopropyl ether to give 6-chloro-3-hydroxymethyl-4-methoxy-2-methyl-1(2H)-isoquinolinone (0.42 g, 66.7%) as crystals.
- 15 Melting point 195-196°C.
- Elemental analysis for  $C_{12}H_{12}NO_3Cl$
- Calculated: C, 56.81; H, 4.77; N, 5.52.
- Found: C, 56.69; H, 4.88; N, 5.44.
- $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 2.70 (1H, bs), 3.71 (3H, s), 3.82 (3H, s),
- 20 4.82 (2H, s), 7.40 (1H, dd,  $J=2.0$ , 8.6 Hz), 7.61 (1H, d,  $J=2.0$  Hz), 8.26 (1H, d,  $J=8.6$  Hz).
- (5) To a solution of 6-chloro-3-hydroxymethyl-4-methoxy-2-methyl-1(2H)-isoquinolinone (0.76 g, 3 mmol) in tetrahydrofuran (20 ml) was added thionyl chloride (0.26
- 25 ml, 3.6 mmol). The obtained mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution, extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and
- 30 concentrated under reduced pressure to give 6-chloro-3-chloromethyl-4-methoxy-2-methyl-1(2H)-isoquinolinone (0.73 g, 90.1%) as crystals.
- $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 3.73 (3H, s), 3.93 (3H, s), 4.80 (2H, s), 7.49 (1H, dd,  $J=2.0$ , 8.6 Hz), 7.74 (1H, d,  $J=2.0$  Hz),
- 35 8.38 (1H, d,  $J=8.6$  Hz).
- (6) A solution of 6-chloro-3-chloromethyl-4-methoxy-2-

methyl-1(2H)-isoquinolinone (0.81 g, 3 mmol) and potassium phthalimide (0.83 g, 4.5 mmol) in N,N-dimethylformamide (20 ml) was stirred at room temperature for 4 h. The reaction mixture was poured  
5 into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 2-((6-chloro-4-  
10 methoxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinoliny)methyl)-1H-isoindole-1,3(2H)-dione (0.59 g, 51.8%) as crystals.

Melting point 248-249°C.

Elemental analysis for  $C_{20}H_{15}N_2O_4Cl$

15 Calculated: C, 62.75; H, 3.95; N, 7.32.

Found: C, 62.73; H, 3.94; N, 7.32.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 3.61 (3H, s), 3.96 (3H, s), 5.07 (2H, s), 7.45 (1H, dd,  $J=2.0$ , 8.6 Hz), 7.73-7.88 (5H, m), 8.36 (1H, d,  $J=8.6$  Hz).

20 (7) To a solution of 2-((6-chloro-4-methoxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinoliny)methyl)-1H-isoindole-1,3(2H)-dione (0.38 g, 1 mmol) in ethanol (10 ml) and tetrahydrofuran (10 ml) was added hydrazine monohydrate (0.14 ml, 3 mmol). The obtained mixture was refluxed  
25 under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. To the  
30 residue was added a solution of 4N hydrogen chloride in ethyl acetate (2 ml), and the precipitated crystals were recrystallized from methanol-diethyl ether to give 3-(aminomethyl)-6-chloro-4-methoxy-2-methyl-1(2H)-isoquinolinone hydrochloride (0.08 g, 28.6%) as crystals.

35 Melting point 236-237°C.

Elemental analysis for  $C_{12}H_{14}N_2O_2Cl_2$



Calculated: C, 49.84; H, 4.88; N, 9.69.

Found: C, 49.67; H, 4.71; N, 9.48.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 3.61 (3H, s), 3.85 (3H, s), 4.24 (2H, s), 7.66 (1H, dd, J=2.0, 8.6 Hz), 7.81 (1H, d, J=2.0 Hz),  
5 8.28 (1H, d, J=8.6 Hz), 8.75 (3H, bs).

#### Example 5

3-(Aminomethyl)-7-chloro-4-methoxy-2-methyl-1(2H)-  
isoquinolinone hydrochloride

(1) Ethyl 7-chloro-4-methoxy-2-methyl-1-oxo-1,2-dihydro-  
10 3-isoquinolinecarboxylate (synthesized according to the  
method similar to that in Example 4 (2))

Melting point 114-115°C.

Elemental analysis for C<sub>14</sub>H<sub>14</sub>NO<sub>4</sub>Cl

Calculated: C, 56.86; H, 4.77; N, 4.74.

15 Found: C, 56.77; H, 4.74; N, 4.64.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.45 (3H, t, J=7.1 Hz), 3.53 (3H, s),  
3.89 (3H, s), 4.49 (2H, q, J=7.1 Hz), 7.67 (1H, dd,  
J=2.0, 8.6 Hz), 7.74 (1H, d, J=8.0 Hz), 8.38 (1H, d,  
J=2.0 Hz).

20 (2) 7-Chloro-4-methoxy-2-methyl-1-oxo-1,2-dihydro-3-  
isoquinolinecarboxylic acid (synthesized according to  
the method similar to that in Example 4 (3))

Melting point 163-164°C.

Elemental analysis for C<sub>12</sub>H<sub>10</sub>NO<sub>4</sub>Cl

25 Calculated: C, 53.85; H, 3.77; N, 5.23.

Found: C, 53.78; H, 3.74; N, 5.03.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 3.60 (3H, s), 3.91 (3H, s), 7.66 (1H, dd,  
J=2.2, 8.8 Hz), 7.76 (1H, d, J=2.2 Hz), 8.40 (1H, d,  
J=2.2 Hz).

30 (3) 7-Chloro-3-hydroxymethyl-4-methoxy-2-methyl-1(2H)-  
isoquinolinone (synthesized according to the method  
similar to that in Example 4 (4))

Melting point 151-152°C.

Elemental analysis for C<sub>12</sub>H<sub>12</sub>NO<sub>3</sub>Cl 1/4H<sub>2</sub>O

35 Calculated: C, 55.83; H, 4.88; N, 5.43.

Found: C, 55.88; H, 4.84; N, 5.55.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:2.57 (1H, bs), 3.73 (3H, s), 3.84 (3H, s), 4.83 (2H, s), 7.59 (1H, dd, J=2.0, 8.6 Hz), 7.66 (1H, d, J=8.6 Hz), 8.33 (1H, d, J=2.0 Hz).

(4) 7-Chloro-3-chloromethyl-4-methoxy-2-methyl-1(2H)-

isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:3.74 (3H, s), 3.93 (3H, s), 4.81 (2H, s), 7.66 (1H, dd, J=2.2, 8.6 Hz), 7.66 (1H, d, J=8.6 Hz), 8.33 (1H, d, J=2.2 Hz).

(5) 2-((7-Chloro-4-methoxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 262-263°C.

Elemental analysis for C<sub>20</sub>H<sub>15</sub>N<sub>2</sub>O<sub>4</sub>Cl

Calculated: C, 62.75; H, 3.95; N, 7.32.

Found: C, 62.41; H, 3.91; N, 7.20.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:3.56 (3H, s), 3.82 (3H, s), 5.02 (2H, s), 7.81-7.86 (6H, m), 8.18 (1H, s).

(6) 3-(Aminomethyl)-7-chloro-4-methoxy-2-methyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 4 (7))

Melting point 225-226°C.

Elemental analysis for C<sub>12</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>Cl<sub>2</sub>

Calculated: C, 49.84; H, 4.88; N, 9.69.

Found: C, 49.82; H, 4.88; N, 10.12.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ:3.62 (3H, s), 3.84 (3H, s), 4.23 (2H, d, J=4.4 Hz), 7.83-7.88 (2H, m), 8.22 (1H, d, J=0.8 Hz), 8.72 (3H, bs).

Example 6

3-(Aminomethyl)-6-chloro-4-isopropoxy-2-methyl-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 6-chloro-4-isopropoxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 4 (2))

Melting point 66-67°C.

Elemental analysis for  $C_{16}H_{18}NO_4Cl$

Calculated: C, 59.35; H, 5.60; N, 4.33.

Found: C, 59.22; H, 5.56; N, 4.33.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.32 (6H, d,  $J=6.2$  Hz), 1.45 (3H, t,  $J=7.2$  Hz), 3.52 (3H, s), 4.28-4.40 (1H, m), 4.47 (2H, q,  $J=7.2$  Hz), 7.50 (1H, dd,  $J=2.0, 8.6$  Hz), 7.75 (1H, d,  $J=2.0$  Hz), 8.37 (1H, d,  $J=8.6$  Hz).

(2) 6-Chloro-4-isopropoxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 229-230°C.

Elemental analysis for  $C_{14}H_{14}NO_4Cl$

Calculated: C, 56.86; H, 4.77; N, 4.74.

Found: C, 56.86; H, 4.79; N, 4.48.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.34 (6H, d,  $J=6.2$  Hz), 3.60 (3H, s), 4.34-4.46 (1H, m), 7.48 (1H, dd,  $J=2.2, 8.4$  Hz), 7.77 (1H, d,  $J=2.2$  Hz), 8.36 (1H, d,  $J=8.4$  Hz).

(3) 6-Chloro-3-hydroxymethyl-4-isopropoxy-2-methyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

Melting point 146-147°C.

Elemental analysis for  $C_{14}H_{16}NO_3Cl$

Calculated: C, 59.68; H, 5.72; N, 4.97.

Found: C, 59.43; H, 5.70; N, 5.06.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.35 (6H, d,  $J=6.2$  Hz), 2.34 (1H, bs), 3.74 (3H, s), 4.12-4.24 (1H, m), 4.83 (2H, d,  $J=4.8$  Hz), 7.41 (1H, d,  $J=8.6$  Hz), 7.61 (1H, s), 8.30 (1H, d,  $J=8.6$  Hz).

(4) 2-((6-Chloro-4-isopropoxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 175-176°C.

Elemental analysis for  $C_{22}H_{19}N_2O_4Cl \cdot 1/2H_2O$

Calculated: C, 62.93; H, 4.80; N, 6.67.

Found: C, 62.78; H, 4.65; N, 6.41.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 1.41 (6H, d,  $J=5.8$  Hz), 3.60 (3H, s), 4.27-4.39 (1H, m), 5.08 (2H, s), 7.43 (1H, dd,  $J=2.0$ , 8.6 Hz), 7.68-7.90 (5H, m), 8.34 (1H, d,  $J=8.6$  Hz).

(5) 3-(Aminomethyl)-6-chloro-4-isopropoxy-2-methyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 4 (7))

Melting point 218-220°C.

Elemental analysis for  $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_2\text{Cl}_2 \cdot 1/2\text{H}_2\text{O}$

10 Calculated: C, 52.27; H, 5.80; N, 8.71.

Found: C, 52.37; H, 5.84; N, 8.70.

$^1\text{H-NMR}(\text{DMSO}-d_6)$   $\delta$ : 1.34 (6H, d,  $J=5.8$  Hz), 3.61 (3H, s), 4.21-4.30 (3H, m), 7.65 (1H, dd,  $J=1.8$ , 8.6 Hz), 7.72 (1H, d,  $J=1.8$  Hz), 8.28 (1H, d,  $J=8.6$  Hz), 8.73 (3H, bs).

15 **Example 7**

3-(Aminomethyl)-4-butoxy-6-chloro-2-methyl-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 4-butoxy-6-chloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 4 (2))

20  $^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 1.01 (3H, t,  $J=7.3$  Hz), 1.45 (3H, t,  $J=7.2$  Hz), 1.51-1.63 (2H, m), 1.73-1.87 (2H, m), 3.52 (3H, s), 3.97 (2H, t,  $J=6.4$  Hz), 4.48 (2H, q,  $J=7.2$  Hz), 7.50 (1H, dd,  $J=2.0$ , 8.6 Hz), 7.71 (1H, d,  $J=2.0$  Hz), 8.38 (1H, d,  $J=8.6$  Hz).

(2) 4-Butoxy-6-chloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 160-161°C.

30 Elemental analysis for  $\text{C}_{15}\text{H}_{16}\text{NO}_4\text{Cl}$

Calculated: C, 58.16; H, 5.21; N, 4.52.

Found: C, 58.34; H, 5.42; N, 4.58.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.95 (3H, t,  $J=7.2$  Hz), 1.39-1.57 (2H, m), 1.67-1.80 (2H, m), 3.43 (3H, s), 3.95 (2H, t,  $J=6.4$  Hz), 7.65 (1H, dd,  $J=2.0$ , 8.6 Hz), 7.73 (1H, d,  $J=2.0$  Hz), 8.26 (1H, d,  $J=8.6$  Hz).

(3) 4-Butoxy-6-chloro-3-hydroxymethyl-2-methyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

Melting point 110-111°C.

5 Elemental analysis for  $C_{15}H_{18}NO_3Cl$

Calculated: C, 60.91; H, 6.18; N, 4.74.

Found: C, 61.06; H, 6.09; N, 4.92.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.03 (3H, t,  $J=7.3$  Hz), 1.50-1.65 (2H, m), 1.76-1.90 (2H, m), 2.82 (1H, bs), 3.69 (3H, s), 3.82 (2H, t,  $J=6.4$  Hz), 4.79 (2H, d,  $J=5.4$  Hz), 7.39 (1H, dd,  $J=2.1, 8.5$  Hz), 7.54 (1H, d,  $J=2.1$  Hz), 8.24 (1H, d,  $J=8.5$  Hz).

(4) 4-Butoxy-6-chloro-3-chloromethyl-2-methyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.05 (3H, t,  $J=7.3$  Hz), 1.56-1.71 (2H, m), 1.83-1.97 (2H, m), 3.73 (3H, s), 3.99 (2H, t,  $J=6.4$  Hz), 4.80 (2H, s), 7.46 (1H, dd,  $J=2.2, 8.6$  Hz), 7.71 (1H, d,  $J=2.2$  Hz), 8.38 (1H, d,  $J=8.6$  Hz).

20 (5) 2-((4-Butoxy-6-chloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl))-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4

(6))

Melting point 200-201°C.

25 Elemental analysis for  $C_{23}H_{21}N_2O_4Cl$

Calculated: C, 65.02; H, 4.98; N, 6.59.

Found: C, 64.85; H, 5.07; N, 6.60.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.93 (3H, t,  $J=7.4$  Hz), 1.40-1.51 (2H, m), 1.70-1.81 (2H, m), 3.52 (3H, s), 3.93 (2H, t,  $J=6.6$  Hz), 5.03 (2H, s), 7.59 (1H, dd,  $J=2.0, 8.4$  Hz), 7.67 (1H, d,  $J=2.0$  Hz), 7.87 (4H, s), 8.25 (1H, d,  $J=8.4$  Hz).

(6) 3-(Aminomethyl)-4-butoxy-6-chloro-2-methyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 4 (7))

35 Melting point 222-223°C.

Elemental analysis for  $C_{15}H_{20}N_2O_2Cl_2 \cdot 1/2H_2O$

Calculated: C, 60.91; H, 6.13; N, 4.74.

Found: C, 61.06; H, 6.09; N, 4.92.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 1.00 (3H, t, J=7.3 Hz), 1.46-1.64 (2H, m), 1.77-1.99 (2H, m), 3.61 (3H, s), 3.91 (2H, t, J=6.4 Hz), 4.23 (2H, bs), 7.65 (1H, dd, J=2.0, 8.6 Hz), 7.72 (1H, d, J=2.0 Hz), 8.28 (1H, d, J=8.6 Hz), 8.74 (3H, bs).

#### Example 8

3-(Aminomethyl)-4-benzyloxy-6-chloro-2-methyl-1(2H)-isoquinolinone hydrochloride

- 10 (1) Ethyl 4-benzyloxy-6-chloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 4 (2))

Melting point 114-115°C.

Elemental analysis for C<sub>20</sub>H<sub>18</sub>NO<sub>4</sub>Cl

- 15 Calculated: C, 64.61; H, 4.88; N, 3.77.

Found: C, 64.67; H, 5.04; N, 4.00.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.35 (3H, t, J=7.2 Hz), 3.54 (3H, s), 3.97 (2H, q, J=7.2 Hz), 5.03 (2H, s), 7.39-7.54 (6H, m), 7.72 (1H, d, J=1.8 Hz), 8.39 (1H, d, J=8.8 Hz).

- 20 (2) 4-Benzyloxy-6-chloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 226-227°C.

Elemental analysis for C<sub>18</sub>H<sub>14</sub>NO<sub>4</sub>Cl

- 25 Calculated: C, 62.89; H, 4.10; N, 4.07.

Found: C, 62.84; H, 4.16; N, 4.20.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 3.61 (3H, s), 5.07 (2H, s), 6.36 (1H, bs), 7.32-7.54 (6H, m), 7.72 (1H, d, J=1.8 Hz), 8.37 (1H, d, J=8.4 Hz).

- 30 (3) 4-Benzyloxy-6-chloro-3-hydroxymethyl-2-methyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

Melting point 207-208°C.

Elemental analysis for C<sub>18</sub>H<sub>16</sub>NO<sub>3</sub>Cl

- 35 Calculated: C, 65.56; H, 4.89; N, 4.25.

Found: C, 65.48; H, 4.96; N, 4.39.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:1.22 (1H, t, J=5.8Hz), 3.64 (3H, s), 4.52 (2H, d, J=5.8Hz), 4.96 (2H, s), 7.35-7.48 (6H, m), 7.72 (1H, d, J=2.2 Hz), 8.36 (1H, d, J=8.4 Hz).

(4) 4-Benzyloxy-6-chloro-3-chloromethyl-2-methyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5)).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:3.74 (3H, s), 4.76 (2H, s), 5.04 (2H, s), 7.43-7.52 (6H, m), 7.75 (1H, d, J=2.2Hz), 8.40 (1H, d, J=8.8 Hz).

(5) 2-(4-Benzyloxy-6-chloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 243-244°C.

Elemental analysis for C<sub>26</sub>H<sub>19</sub>N<sub>2</sub>O<sub>4</sub>Cl H<sub>2</sub>O

Calculated: C, 65.48; H, 4.44; N, 5.87.

Found: C, 65.27; H, 4.22; N, 5.99.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ:3.48 (3H, s), 5.06 (4H, s), 7.38-7.64 (7H, m), 7.85 (4H, s), 8.25 (1H, d, J=8.6 Hz).

(6) 3-(Aminomethyl)-4-benzyloxy-6-chloro-2-methyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 4 (7))

Melting point 221-223°C.

Elemental analysis for C<sub>18</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>Cl<sub>2</sub> 1/2H<sub>2</sub>O

Calculated: C, 52.95; H, 6.22; N, 8.23.

Found: C, 53.21; H, 6.25; N, 8.28.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ:3.62 (3H, s), 4.25 (2H, s), 5.02 (2H, s), 7.42-7.52 (7H, m), 7.59-7.69 (4H, m), 8.29 (1H, d, J=8.4 Hz), 8.72 (3H, bs).

### Example 9

3-(Aminomethyl)-6-chloro-2-methyl-4-(2-quinolinylmethoxy)-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 6-chloro-2-methyl-1-oxo-4-(2-quinolinylmethoxy)-1,2-dihydro-3-isoquinolinecarboxylate

(synthesized according to the method similar to that in Example 4 (2))

Melting point 164-165°C.

Elemental analysis for  $C_{23}H_{19}N_2O_4Cl$

Calculated: C, 65.33; H, 4.53; N, 6.62.

Found: C, 65.29; H, 4.52; N, 6.33.

- 5  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.31 (3H, t,  $J=7.1$  Hz), 3.56 (3H, s),  
4.39 (2H, q,  $J=7.1$  Hz), 5.33 (2H, s), 7.52 (1H, dd,  
 $J=1.9, 8.6$  Hz), 7.55-7.63 (1H, m), 7.72-7.82 (2H, m),  
7.88 (1H, d,  $J=8.4$  Hz), 7.93 (1H, d,  $J=1.9$  Hz), 8.11 (1H,  
10 d,  $J=8.6$  Hz), 8.29 (1H, d,  $J=8.4$  Hz), 8.41 (1H, d,  $J=8.4$   
Hz).

(2) 6-Chloro-2-methyl-1-oxo-4-(2-quinolinylmethoxy)-1,2-  
dihydro-3-isoquinolinecarboxylic acid (synthesized  
according to the method similar to that in Example 4  
(3))

- 15 Melting point 268-268°C.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 3.51 (3H, s), 5.29 (2H, s), 7.43 (1H,  
dd,  $J=2.0, 8.8$  Hz), 7.59-7.67 (1H, m), 7.75-7.84 (2H, m),  
7.87 (1H, d,  $J=8.6$  Hz), 8.00-8.06 (2H, m), 8.19 (1H, d,  
 $J=8.6$  Hz), 8.46 (1H, d,  $J=8.8$  Hz).

- 20 (3) 6-Chloro-3-hydroxymethyl-2-methyl-4-(2-  
quinolinylmethoxy)-1(2H)-isoquinolinone (synthesized  
according to the method similar to that in Example 4  
(4))

Melting point 206-207°C.

- 25 Elemental analysis for  $C_{21}H_{17}N_2O_3Cl \cdot 1/4H_2O$

Calculated: C, 65.46; H, 4.58; N, 7.27.

Found: C, 65.40; H, 4.47; N, 7.23.

- $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 3.78 (3H, s), 4.80 (2H, s), 5.27 (2H, s),  
7.42 (1H, dd,  $J=2.0, 8.6$  Hz), 7.57-7.93 (5H, m), 8.12  
30 (1H, d,  $J=8.8$  Hz), 8.30 (1H, d,  $J=8.6$  Hz), 8.36 (1H, d,  
 $J=8.8$  Hz).

(4) 6-Chloro-3-chloromethyl-2-methyl-4-(2-  
quinolinylmethoxy)-1(2H)-isoquinolinone (synthesized  
according to the method similar to that in Example 4

- 35 (5))

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 3.76 (3H, s), 4.89 (2H, s), 5.33 (2H, s),



7.50 (1H, dd, J=2.0, 8.4 Hz), 7.57-7.65 (1H, m), 7.74-7.92 (3H, m), 7.95 (1H, d, J=2.0 Hz), 8.16 (1H, d, J=8.4 Hz), 8.31 (1H, d, J=8.4 Hz), 8.41 (1H, d, J=8.4 Hz).

(5) 2-((6-Chloro-2-methyl-1-oxo-4-(2-quinolinylmethoxy)-1,2-dihydro-3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 249-250°C.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 3.53 (3H, s), 5.16 (2H, s), 5.30 (2H, s), 7.59-7.67 (2H, m), 7.80-7.83 (6H, m), 8.00-8.08 (3H, m), 8.27 (1H, d, J=9.0 Hz), 8.46 (1H, d, J=8.4 Hz).

(6) 3-(Aminomethyl)-6-chloro-2-methyl-4-(2-quinolinylmethoxy)-1(2H)-isoquinolinone dihydrochloride (synthesized according to the method similar to that in Example 4 (7))

Melting point 236°C.

Elemental analysis for C<sub>21</sub>H<sub>20</sub>N<sub>3</sub>O<sub>2</sub>Cl<sub>3</sub> 1/4H<sub>2</sub>O

Calculated: C, 55.16; H, 4.52; N, 9.19.

Found: C, 55.29; H, 4.54; N, 9.12.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 3.65 (3H, s), 4.41 (2H, d, J=4.8 Hz), 5.44 (2H, s), 7.67 (1H, dd, J=2.0, 8.8 Hz), 7.17 (1H, t, J=7.3 Hz), 7.96 (1H, t, J=7.3 Hz), 8.07 (1H, d, J=8.6 Hz), 8.15-8.20 (2H, m), 8.30 (1H, d, J=8.8 Hz), 8.33 (1H, d, J=8.4 Hz), 8.75 (1H, d, J=8.4 Hz), 8.87 (3H, bs).

#### Example 10

3-(Aminomethyl)-6-chloro-2-methyl-4-(2-phenylethoxy)-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 6-chloro-2-methyl-1-oxo-4-(2-phenylethoxy)-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.38 (3H, t, J=7.2 Hz), 3.09 (2H, t, J=6.4 Hz), 3.49 (3H, s), 4.17 (2H, t, J=6.4 Hz), 4.33 (2H, q, J=7.2 Hz), 7.24-7.40 (6H, m), 7.44 (1H, dd, J=2.1, 8.5 Hz), 8.33 (1H, d, J=8.5 Hz).

(2) 6-Chloro-2-methyl-1-oxo-4-(2-phenylethoxy)-1,2-

dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 168-169°C.

5 Elemental analysis for  $C_{19}H_{16}NO_4Cl$

Calculated: C, 63.78; H, 4.51; N, 3.91.

Found: C, 63.73; H, 4.56; N, 3.86.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 3.06 (2H, t, J=6.4 Hz), 3.43 (3H, s), 4.16 (2H, t, J=6.4 Hz), 7.19 (1H, dd, J=2.0 Hz), 7.28-7.36 (5H, m), 7.58 (1H, dd, J=2.0, 8.6 Hz), 8.20 (1H, d, J=8.6 Hz).

(3) 6-Chloro-3-hydroxymethyl-2-methyl-4-(2-phenylethoxy)-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4

15 (4))

Melting point 170-171°C.

Elemental analysis for  $C_{19}H_{18}NO_3Cl$

Calculated: C, 66.38; H, 5.28; N, 4.07.

Found: C, 66.18; H, 5.20; N, 3.93.

20  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 2.08 (1H, bs), 3.14 (2H, t, J=6.2 Hz), 3.67 (3H, s), 4.08 (2H, t, J=6.2 Hz), 4.59 (2H, d, J=5.8 Hz), 7.26-7.43 (7H, m), 8.27 (1H, d, J=8.4 Hz).

(4) 6-Chloro-3-chloromethyl-2-methyl-4-(2-phenylethoxy)-1(2H)-isoquinolinone (synthesized according to the

25 method similar to that in Example 4 (5))

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 3.19 (2H, t, J=6.4 Hz), 3.69 (3H, s), 4.20 (2H, t, J=6.4 Hz), 4.58 (2H, s), 7.34-7.42 (6H, m), 7.46 (1H, d, J=2.2 Hz), 8.34 (1H, d, J=8.0 Hz).

(5) 2-((6-Chloro-2-methyl-1-oxo-4-(2-phenylethoxy)-1,2-dihydro-3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 219-220°C.

Elemental analysis for  $C_{27}H_{21}N_2O_4Cl$

35 Calculated: C, 68.57; H, 4.48; N, 5.92.

Found: C, 68.29; H, 4.54; N, 5.97.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ:3.06 (2H, t, J=6.4 Hz), 3.49 (3H, s), 4.14 (2H, t, J=6.4 Hz), 4.96 (2H, s), 7.19-7.30 (6H, m), 7.52 (1H, dd, J=2.2, 8.6 Hz), 7.89 (4H, s), 8.19 (1H, d, J=8.6 Hz).

- 5 (6) Tert-butyl (6-chloro-2-methyl-1-oxo-4-(2-phenylethoxy)-1,2-dihydro-3-isoquinoliny)l)methylcarbamate (synthesized according to the method similar to that in Example 1 (6)).  
Melting point 163-164°C.

10 Elemental analysis for C<sub>24</sub>H<sub>27</sub>N<sub>2</sub>O<sub>4</sub>Cl

Calculated: C, 65.08; H, 6.14; N, 6.32.

Found: C, 65.16; H, 6.32; N, 6.15.

- <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:1.47 (9H, s), 3.15 (2H, t, J=6.4 Hz), 3.59 (3H, s), 4.04 (2H, t, J=6.4 Hz), 4.34 (2H, d, J=6.0 Hz), 4.60 (1H, bs), 7.27-7.41 (7H, m), 8.29 (1H, d, J=8.8 Hz).

- (7) 3-(Aminomethyl)-6-chloro-2-methyl-4-(2-phenylethoxy)-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7)).

20 Melting point 200-201°C.

Elemental analysis for C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>Cl<sub>2</sub> 3/4H<sub>2</sub>O

Calculated: C, 58.10; H, 5.52; N, 7.13.

Found: C, 58.23; H, 5.77; N, 7.11.

- 25 <sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ:3.16 (2H, t, J=6.4 Hz), 3.58 (3H, s), 4.11 (2H, t, J=6.4 Hz), 4.25 (2H, d, J=5.6 Hz), 7.21 (1H, d, J=2.0 Hz), 7.29-7.45 (5H, m), 7.58 (1H, dd, J=2.0, 8.6 Hz), 8.22 (1H, d, J=8.6 Hz), 8.68 (3H, bs).

#### Example 11

- 30 3-(Aminomethyl)-6-chloro-2-methyl-4-(1-naphthylmethoxy)-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 6-chloro-2-methyl-4-(1-naphthylmethoxy)-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1

- 35 (2))

Melting point 158-159°C.

Elemental analysis for  $C_{24}H_{20}NO_4Cl$

Calculated: C, 68.33; H, 4.78; N, 3.32.

Found: C, 68.25; H, 4.559; N, 3.21.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.24 (3H, t,  $J=7.2$  Hz), 3.53 (3H, s),

5 4.19 (2H, q,  $J=7.2$  Hz), 5.50 (2H, s), 7.45-7.63 (5H, m),  
7.68 (1H, d,  $J=2.2$  Hz), 7.87-7.95 (2H, m), 8.09-8.14 (1H,  
m), 8.39 (1H, d,  $J=8.4$  Hz).

(2) 6-Chloro-2-methyl-4-(1-naphthylmethoxy)-1-oxo-1,2-  
dihydro-3-isoquinolinecarboxylic acid (synthesized

10 according to the method similar to that in Example 4  
(3))

Melting point 166-167°C.

Elemental analysis for  $C_{22}H_{16}NO_4Cl$

Calculated: C, 67.10; H, 4.10; N, 3.56.

15 Found: C, 66.93; H, 3.95; N, 3.49.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 3.50 (3H, s), 5.49 (2H, s), 7.51-7.68  
(6H, m), 7.96-8.04 (2H, m), 8.20-8.28 (2H, m).

(3) 6-Chloro-3-hydroxymethyl-2-methyl-4-(1-  
naphthylmethoxy)-1(2H)-isoquinolinone (synthesized

20 according to the method similar to that in Example 4.  
(4))

Melting point 202-203°C.

Elemental analysis for  $C_{22}H_{18}NO_3Cl$

Calculated: C, 69.57; H, 4.78; N, 3.69.

25 Found: C, 69.18; H, 5.11; N, 3.61.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 3.64 (3H, s), 4.63 (2H, d,  $J=5.0$  Hz),  
5.47 (2H, s), 5.59 (1H, t,  $J=5.0$  Hz), 7.50-7.69 (6H, m),  
7.96-8.04 (2H, m), 8.21-8.25 (2H, m).

(4) 6-Chloro-3-chloromethyl-2-methyl-4-(1-

30 naphthylmethoxy)-1(2H)-isoquinolinone (synthesized  
according to the method similar to that in Example 4  
(5))

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 3.72 (3H, s), 4.67 (2H, s), 5.52 (2H, s),  
7.45-7.67 (6H, m), 7.71 (1H, d,  $J=1.8$  Hz), 7.89-7.97 (2H,  
35 m), 8.16 (1H, d,  $J=8.0$  Hz), 8.39 (1H, d,  $J=8.4$  Hz).

(5) 2-((6-Chloro-2-methyl-4-(1-naphthylmethoxy)-1-oxo-

1,2-dihydro-3-isoquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 211-212°C.

- 5 <sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ:3.49 (3H, s), 5.09 (2H, s), 5.58 (2H, s), 7.45-7.68 (6H, m), 7.84 (4H, s), 7.91-8.01 (2H, m), 8.14-8.19 (1H, m), 8.23 (1H, d, J=8.8 Hz).

(6) Tert-butyl (6-chloro-2-methyl-4-(1-naphthylmethoxy)-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate

- 10 (synthesized according to the method similar to that in Example 1 (6))

Melting point 205-206°C.

Elemental analysis for C<sub>27</sub>H<sub>27</sub>N<sub>2</sub>O<sub>4</sub>Cl

Calculated: C, 67.71; H, 5.68; N, 5.85.

- 15 Found: C, 67.50; H, 5.90; N, 5.70.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:1.37 (9H, s), 3.14 (1H, bs), 3.45 (3H, s), 4.02 (2H, d, J=6.2 Hz), 5.44 (2H, s), 7.29 (1H, d, J=7.2 Hz), 7.41-7.51 (2H, m), 7.72 (1H, d, J=2.0 Hz), 7.55-7.69 (2H, m), 7.81 (1H, d, J=1.8 Hz), 7.91-7.95 (2H, m), 8.24 (1H, d, J=8.2 Hz), 8.39 (1H, d, J=8.8 Hz).

(7) 3-(Aminomethyl)-6-chloro-2-methyl-4-(1-naphthylmethoxy)-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

- 25 Melting point 226-227°C.

Elemental analysis for C<sub>22</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>Cl<sub>2</sub> 1/4H<sub>2</sub>O

Calculated: C, 62.94; H, 4.92; N, 6.67.

Found: C, 63.01; H, 4.79; N, 6.59.

- <sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ:3.65 (3H, s), 4.29 (2H, d, J=4.2 Hz), 5.55 (2H, s), 7.52-7.78 (6H, m), 7.98-8.06 (2H, m), 8.22-8.30 (2H, m), 8.81 (3H, bs).

#### Example 12

3-(Aminomethyl)-7-chloro-2-methyl-4-phenyl-1(2H)-isoquinolinone hydrochloride

- 35 (1) To a solution of ethyl 7-chloro-4-hydroxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized

according to the method similar to that in Example 5 (1)) (2.82 g, 10 mmol) in tetrahydrofuran (20 ml) was added sodium hydride (0.48 g, 12 mmol) (60% in oil) at 0°C and the mixture was stirred at 0°C for 30 min. To the obtained mixture was added N-phenyltrifluoromethane sulfonimide (4.29 g, 12 mmol) and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give ethyl 7-chloro-2-methyl-1-oxo-4-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinecarboxylate (2.95 g, 71.4%) as an oil.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.45 (3H, d, J=7.2 Hz), 3.61 (3H, s), 4.49 (2H, q, J=7.2 Hz), 7.75-7.76 (2H, m), 8.44-8.45 (1H, m).

(2) A mixture of ethyl 7-chloro-2-methyl-1-oxo-4-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinecarboxylate (2.90 g, 7 mmol), phenylboronic acid (1.02 g, 8.4 mmol) and sodium carbonate (1.85 g, 17.5 mmol) in toluene (20 ml), ethanol (4 ml) and water (4 ml) was stirred under an argon atmosphere at room temperature for 30 min. To the obtained mixture was added tetrakis(triphenylphosphine)palladium (0.46 g, 4 mmol) and the mixture was refluxed under heating under an argon atmosphere for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give ethyl 7-chloro-2-methyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinecarboxylate (1.70 g, 71.1%) as crystals. Melting point 152-153°C.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.92 (3H, t, J=7.1 Hz), 3.62 (3H, s), 4.02 (2H, q, J=7.1 Hz), 7.17 (1H, dd, J=8.8 Hz), 7.28-7.33 (2H, m), 7.41-7.53 (4H, m), 8.48 (1H, d, J=2.2 Hz).

- (3) 7-Chloro-2-methyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 261-262°C.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:3.68 (3H, s), 7.13 (1H, d, J=8.8 Hz), 7.32-7.51 (6H, m), 8.45 (1H, d, J=2.2 Hz).

- (4) 7-Chloro-3-hydroxymethyl-2-methyl-4-phenyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

Melting point 199-200°C.

Elemental analysis for C<sub>17</sub>H<sub>14</sub>NO<sub>2</sub>Cl

- Calculated: C, 68.12; H, 4.71; N, 4.67.

Found: C, 68.25; H, 4.71; N, 4.49.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:2.17 (1H, t, J=5.5 Hz), 3.82 (3H, s), 4.40 (2H, d, J=5.5 Hz), 6.96 (1H, d, J=8.8 Hz), 7.26-7.33 (2H, m), 7.39 (1H, dd, J=2.2, 8.8 Hz), 7.45-7.54

- (3H, m), 8.39 (1H, d, J=2.2 Hz).

(5) 7-Chloro-3-chloromethyl-2-methyl-4-phenyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

- <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:3.84 (3H, s), 4.40 (2H, s), 6.99 (1H, d, J=8.4 Hz), 7.31-7.35 (2H, m), 7.42-7.56 (4H, m), 8.47 (1H, d, J=2.2 Hz).

(6) 2-((7-Chloro-2-methyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-dione

- (synthesized according to the method similar to that in Example 4 (6))

Melting point 241-242°C.

Elemental analysis for C<sub>25</sub>H<sub>17</sub>N<sub>2</sub>O<sub>3</sub>Cl

Calculated: C, 70.01; H, 4.00; N, 6.53.

Found: C, 69.69; H, 4.13; N, 6.56.

- <sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ:3.61 (3H, s), 4.76 (2H, s), 6.89 (1H, d, J=8.8 Hz), 7.26-7.31 (2H, m), 7.40-7.43 (3H, m), 7.66

(1H, dd, J=2.2, 8.8 Hz), 7.74-7.83 (4H, m), 8.23 (1H, d, J=2.2 Hz).

(7) 3-(Aminomethyl)-7-chloro-2-methyl-4-phenyl-1(2H)-isoquinolinone hydrochloride (synthesized according to

5 the method similar to that in Example 4 (7))

Melting point 242-243°C.

Elemental analysis for  $C_{17}H_{16}N_2OCl_2 \cdot 1/2H_2O$

Calculated: C, 59.31; H, 4.98; N, 8.14.

Found: C, 59.50; H, 4.97; N, 8.14.

10  $^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 3.72 (3H, s), 3.93 (2H, s), 6.94 (1H, d, J=8.6 Hz), 7.37-7.41 (2H, m), 7.56-7.59 (3H, m), 7.72 (1H, dd, J=2.4, 8.6 Hz), 8.27 (1H, d, J=2.4 Hz), 8.65 (3H, bs).

### Example 13

15 3-(Aminomethyl)-6-chloro-2-methyl-4-propoxy-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 6-chloro-2-methyl-4-propoxy-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))

20  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.08 (3H, t, J=7.3 Hz), 1.45 (3H, t, J=7.2 Hz), 1.76-1.89 (2H, m), 3.51 (3H, s), 3.93 (2H, t, J=6.6 Hz), 4.48 (2H, q, J=7.2 Hz), 7.49 (1H, dd, J=2.0, 8.6 Hz), 7.71 (1H, d, J=2.0 Hz), 8.37 (1H, d, J=8.6 Hz).

(2) 6-Chloro-2-methyl-1-oxo-4-propoxy-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 164-165°C.

Elemental analysis for  $C_{14}H_{14}NO_4Cl$

Calculated: C, 56.86; H, 4.77; N, 4.74.

30 Found: C, 56.82; H, 4.70; N, 4.52.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.08 (3H, t, J=7.3 Hz), 1.77-1.95 (2H, m), 3.65 (3H, s), 3.97 (2H, t, J=6.6 Hz), 7.51 (1H, dd, J=2.0, 8.6 Hz), 7.64 (1H, d, J=2.0 Hz), 7.67 (1H, bs), 8.31 (1H, d, J=8.6 Hz).

35 (3) 6-Chloro-3-hydroxymethyl-2-methyl-4-propoxy-1(2H)-isoquinolinone (synthesized according to the method



similar to that in Example 4 (4))

Melting point 95.5-96.5°C.

Elemental analysis for  $C_{14}H_{16}NO_3Cl$

Calculated: C, 59.68; H, 5.72; N, 4.97.

5 Found: C, 59.38; H, 5.69; N, 4.87.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.14 (3H, t,  $J=7.3$  Hz), 1.79-1.93 (2H, m),  
2.89 (1H, bs), 3.69 (3H, s), 3.79 (2H, t,  $J=6.6$  Hz),  
4.79 (2H, d,  $J=4.8$  Hz), 7.39 (1H, dd,  $J=2.0, 8.6$  Hz),  
7.55 (1H, d,  $J=2.0$  Hz), 8.24 (1H, dd,  $J=3.8, 8.6$  Hz).

10 (4) 6-Chloro-3-chloromethyl-2-methyl-4-propoxy-1(2H)-  
isoquinolinone (synthesized according to the method  
similar to that in Example 4 (5))

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.16 (3H, t,  $J=7.3$  Hz), 1.86-2.00 (2H, m),  
3.73 (3H, s), 3.95 (2H, t,  $J=6.6$  Hz), 4.80 (2H, s), 7.48  
15 (1H, dd,  $J=2.0, 8.6$  Hz), 7.71 (1H, d,  $J=2.0$  Hz), 8.38  
(1H, d,  $J=8.6$  Hz).

(5) 2-((6-Chloro-2-methyl-4-propoxy-1-oxo-1,2-dihydro-3-  
isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-dione  
(synthesized according to the method similar to that in

20 Example 4 (6))

Melting point 193-194°C.

Elemental analysis for  $C_{22}H_{19}N_2O_4Cl$

Calculated: C, 64.31; H, 4.66; N, 6.82.

Found: C, 63.96; H, 4.51; N, 6.48.

25  $^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 1.00 (3H, t,  $J=7.4$  Hz), 1.72-1.86 (2H,  
m), 3.51 (3H, s), 3.90 (2H, t,  $J=6.7$  Hz), 5.03 (2H, s),  
7.59 (1H, dd,  $J=1.8, 8.4$  Hz), 7.68 (1H, d,  $J=1.8$  Hz),  
7.86 (4H, s), 8.24 (1H, d,  $J=8.4$  Hz).

(6) Tert-butyl (6-chloro-2-methyl-4-propoxy-1-oxo-1,2-  
30 dihydro-3-isoquinolinyl)methylcarbamate (synthesized  
according to the method similar to that in Example 1  
(6))

Melting point 104-105°C.

Elemental analysis for  $C_{19}H_{25}N_2O_4Cl$

35 Calculated: C, 59.92; H, 6.62; N, 7.36.

Found: C, 59.87; H, 6.34; N, 7.23.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:1.13 (3H, t, J=7.4 Hz), 1.47 (9H, s), 1.85-1.96 (2H, m), 3.62 (3H, s), 3.80 (2H, t, J=6.6 Hz), 4.53 (2H, d, J=6.0 Hz), 4.77 (1H, bs), 7.43 (1H, dd, J=2.0, 8.6 Hz), 7.65 (1H, d, J=2.0 Hz), 8.33 (1H, d,

5 J=8.6 Hz).

(7) 3-(Aminomethyl)-6-chloro-2-methyl-4-propoxy-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 226-227°C.

10 Elemental analysis for C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>Cl<sub>2</sub> 1/2H<sub>2</sub>O

Calculated: C, 51.55; H, 5.87; N, 8.59.

Found: C, 51.61; H, 6.13; N, 8.44.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ:1.09 (3H, t, J=7.4 Hz), 1.79-1.93 (2H, m), 3.39 (3H, s), 3.88 (2H, t, J=6.4 Hz), 4.24 (2H, s), 7.66 (1H, dd, J=2.0, 8.6 Hz), 7.74 (1H, d, J=2.0 Hz), 8.28 (1H, d, J=8.6 Hz), 8.78 (3H, bs).

15

#### Example 14

3-(Aminomethyl)-6-chloro-4-cyclopentylmethoxy-2-methyl-1(2H)-isoquinolinone hydrochloride

20

(1) Ethyl 6-chloro-4-cyclopentylmethoxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))

Melting point 89-90°C.

25

Elemental analysis for C<sub>19</sub>H<sub>22</sub>NO<sub>4</sub>Cl 1/4H<sub>2</sub>O

Calculated: C, 61.96; H, 6.15; N, 3.80.

Found: C, 61.91; H, 6.03; N, 3.93.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:1.33-1.43 (2H, m), 1.45 (3H, t, J=7.2 Hz), 1.61-1.72 (4H, m), 1.89-1.93 (2H, m), 2.32-2.47 (1H, m), 3.51 (3H, s), 3.85 (2H, d, J=6.8 Hz), 4.47 (2H, q, J=7.2 Hz), 7.50 (1H, dd, J=2.0, 8.6 Hz), 7.72 (1H, d, J=2.0 Hz), 8.37 (1H, d, J=8.6 Hz).

30

(2) 6-Chloro-4-cyclopentylmethoxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized

35

according to the method similar to that in Example 4 (3))

Melting point 191-192°C.

Elemental analysis for  $C_{17}H_{16}NO_4Cl \cdot 1/4H_2O$

Calculated: C, 60.00; H, 5.48; N, 4.12.

Found: C, 60.20; H, 5.28; N, 4.09.

5  $^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 1.33-1.46 (2H, m), 1.58-1.60 (4H, m),  
1.71-1.86 (2H, m), 2.30-2.45 (1H, m), 3.43 (3H, s), 3.82  
(2H, d, J=6.8 Hz), 7.65 (1H, dd, J=2.0, 8.6 Hz), 7.71  
(1H, d, J=2.0 Hz), 8.26 (1H, d, J=8.6 Hz)

(3) 6-Chloro-4-cyclopentylmethoxy-3-hydroxymethyl-2-  
10 methyl-1(2H)-isoquinolinone (synthesized according to  
the method similar to that in Example 4 (4)).

Melting point 127-128°C.

Elemental analysis for  $C_{17}H_{20}NO_3Cl \cdot 1/4H_2O$

Calculated: C, 62.57; H, 6.33; N, 4.29.

15 Found: C, 62.61; H, 6.21; N, 4.23.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.35-1.51 (2H, m), 1.61-1.74 (4H, m),  
1.84-1.97 (2H, m), 2.36-2.51 (1H, m), 3.71 (5H, s), 4.81  
(2H, d, J=5.0 Hz), 7.40 (1H, dd, J=2.0, 8.6 Hz), 7.60  
(1H, d, J=2.0 Hz), 8.28 (1H, d, J=8.6 Hz).

20 (4) 6-Chloro-3-chloromethyl-4-cyclopentylmethoxy-2-  
methyl-1(2H)-isoquinolinone (synthesized according to  
the method similar to that in Example 4 (5))

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.36-1.71 (6H, m), 1.85-1.97 (2H, m),  
2.37-2.57 (1H, m), 3.73 (3H, s), 3.87 (2H, d, J=7.0 Hz),  
25 4.80 (2H, s), 7.48 (1H, dd, J=2.2, 8.8 Hz), 7.72 (1H, d,  
J=2.2 Hz), 8.37 (1H, d, J=8.8 Hz).

(5) 2-((6-Chloro-4-cyclopentylmethoxy-2-methyl-1-oxo-  
1,2-dihydro-3-isoquinolinyl)methyl)-1H-isoindole-  
1,3(2H)-dione (synthesized according to the method  
30 similar to that in Example 4 (6))

Melting point 204-205°C.

Elemental analysis for  $C_{25}H_{23}N_2O_4Cl \cdot 3/4H_2O$

Calculated: C, 64.65; H, 5.32; N, 6.03.

Found: C, 64.85; H, 5.08; N, 6.09.

35  $^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 1.23-1.63 (6H, m), 1.72-1.84 (2H, m),  
2.33-2.46 (1H, m), 3.48 (3H, s), 3.83 (2H, d, J=6.8 Hz),

7.59 (1H, dd, J=2.0, 8.6 Hz), 7.68 (1H, d, J=2.0 Hz),  
7.82-7.91 (4H, m), 8.37 (1H, d, J=8.8 Hz).

(6) Tert-butyl (6-chloro-4-cyclopentylmethoxy-2-methyl-  
1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate

5 (synthesized according to the method similar to that in  
Example 1 (6))

Melting point 161-162°C.

Elemental analysis for  $C_{22}H_{29}N_2O_4Cl$

Calculated: C, 62.77; H, 6.94; N, 6.66.

10 Found: C, 62.49; H, 7.15; N, 6.60.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.26-1.44 (2H, m), 1.47 (9H, s), 1.60-  
1.71 (4H, m), 1.87-1.99 (2H, m), 2.38-2.53 (1H, m), 3.62  
(3H, s), 3.72 (2H, d, J=6.8 Hz), 4.53 (2H, d, J=5.8 Hz),  
7.43 (1H, dd, J=1.8, 8.6 Hz), 7.66 (1H, d, J=1.8 Hz),  
15 8.33 (1H, d, J=8.6 Hz).

(7) 3-(Aminomethyl)-6-chloro-4-cyclopentylmethoxy-2-  
methyl-1(2H)-isoquinolinone hydrochloride (synthesized  
according to the method similar to that in Example 1  
(7))

20 Melting point 217-219°C.

Elemental analysis for  $C_{17}H_{22}N_2O_2Cl_2 \cdot 1/2H_2O$

Calculated: C, 55.74; H, 6.33; N, 7.65.

Found: C, 55.75; H, 6.32; N, 7.69.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 1.37-1.68 (6H, m), 1.81-1.93 (2H, m),  
25 2.39-2.54 (1H, m), 3.61 (3H, s), 3.80 (2H, d, J=6.8 Hz),  
4.24 (2H, d, J=5.2 Hz), 7.65 (1H, dd, J=2.0, 8.4 Hz),  
7.72 (1H, d, J=2.0 Hz), 8.28 (1H, d, J=8.4 Hz), 8.77 (3H,  
bs).

#### Example 15

30 3-(Aminomethyl)-6-chloro-2-methyl-4-(4-nitrophenoxy)-  
1(2H)-isoquinolinone hydrochloride

(1) Ethyl 6-chloro-2-methyl-4-(4-nitrophenoxy)-1-oxo-  
1,2-dihydro-3-isoquinolinecarboxylate (synthesized  
according to the method similar to that in Example 4

35 (2))

Melting point 184-185°C.

Elemental analysis for  $C_{19}H_{15}N_2O_6Cl \cdot 1/4H_2O$

Calculated: C, 56.66; H, 3.75; N, 6.95.

Found: C, 56.70; H, 3.85; N, 6.81.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.12 (3H, t,  $J=7.2$  Hz), 3.60 (3H, s),  
5 4.28 (2H, q,  $J=7.2$  Hz), 7.05 (2H, d,  $J=9.2$  Hz), 7.35 (1H,  
d,  $J=2.0$  Hz), 7.55 (1H, dd,  $J=2.0, 8.8$  Hz), 8.24 (2H, d,  
 $J=9.2$  Hz), 8.44 (1H, d,  $J=8.8$  Hz).

(2) 6-Chloro-2-methyl-4-(4-nitrophenoxy)-1-oxo-1,2-  
dihydro-3-isoquinolinecarboxylic acid (synthesized  
10 according to the method similar to that in Example 4  
(3)).

Melting point 240-241°C.

Elemental analysis for  $C_{17}H_{11}N_2O_6Cl \cdot 1/2AcOEt$

Calculated: C, 54.49; H, 3.61; N, 6.69.

15 Found: C, 54.63; H, 3.64; N, 6.69.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 3.51 (3H, s), 7.28 (2H, d,  $J=9.2$  Hz),  
7.36 (1H, d,  $J=2.0$  Hz), 7.68 (1H, d,  $J=2.0, 8.6$  Hz),  
8.22 (2H, d,  $J=9.2$  Hz), 8.33 (1H, d,  $J=8.6$  Hz).

(3) 6-Chloro-3-hydroxymethyl-2-methyl-4-(4-  
20 nitrophenoxy)-1(2H)-isoquinolinone (synthesized  
according to the method similar to that in Example 4  
(4)).

Melting point 249-250°C.

Elemental analysis for  $C_{17}H_{13}N_2O_5Cl$

25 Calculated: C, 56.60; H, 3.63; N, 7.77.

Found: C, 56.68; H, 3.83; N, 7.65.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 3.80 (3H, s), 4.35 (1H, bs), 4.64 (2H, d,  
 $J=5.2$  Hz), 7.07 (2H, d,  $J=9.1$  Hz), 7.32 (1H, d,  $J=2.0$   
Hz), 7.47 (1H, dd,  $J=2.0, 8.6$  Hz), 8.22 (2H, d,  $J=9.1$   
30 Hz), 8.40 (1H, d,  $J=8.6$  Hz).

(4) 6-Chloro-3-chloromethyl-2-methyl-4-(4-nitrophenoxy)-  
1(2H)-isoquinolinone (synthesized according to the  
method similar to that in Example 4 (5))

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 3.79 (3H, s), 4.65 (2H, s), 7.06 (2H, d,  
35  $J=9.1$  Hz), 7.34 (1H, d,  $J=1.8$  Hz), 7.52 (1H, dd,  $J=1.8,$   
8.8 Hz), 8.24 (2H, d,  $J=9.1$  Hz), 8.44 (1H, d,  $J=8.8$  Hz).

(5) 2-((6-Chloro-2-methyl-4-(4-nitrophenoxy)-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

5 Melting point 257-258°C.

Elemental analysis for  $C_{25}H_{16}N_3O_6Cl$

Calculated: C, 61.30; H, 3.29; N, 8.58.

Found: C, 61.10; H, 3.38; N, 8.41.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 3.81 (3H, s), 4.94 (2H, s), 6.92 (2H, d, J=9.4 Hz), 7.24 (1H, d, J=1.8 Hz), 7.60-7.72 (5H, m), 7.88 (2H, d, J=9.4 Hz), 8.33 (1H, d, J=8.4 Hz).

(6) Tert-butyl [6-chloro-2-methyl-4-(4-nitrophenoxy)-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate

(synthesized according to the method similar to that in

15 Example 1 (6))

Melting point 198-199°C.

Elemental analysis for  $C_{22}H_{22}N_3O_6Cl$

Calculated: C, 57.46; H, 4.82; N, 9.14.

Found: C, 57.44; H, 4.80; N, 9.25.

20  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.41 (9H, s), 3.70 (3H, s), 4.41 (2H, d, J=5.8 Hz), 4.64 (1H, bs), 7.03 (2H, d, J=9.4 Hz), 7.29 (1H, d, J=2.0 Hz), 7.48 (1H, d, J=2.0, 8.6 Hz), 8.24 (2H, d, J=9.4 Hz), 8.40 (1H, d, J=8.6 Hz).

(7) 3-(Aminomethyl)-6-chloro-2-methyl-4-(4-

25 nitrophenoxy)-1(2H)-isoquinolinone hydrochloride

(synthesized according to the method similar to that in

Example 1 (7))

Melting point 242-243°C.

Elemental analysis for  $C_{17}H_{15}N_3O_4Cl_2 \cdot 1/4H_2O$

30 Calculated: C, 50.95; H, 3.90; N, 10.49.

Found: C, 51.05; H, 3.92; N, 10.23.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 3.68 (3H, s), 4.08 (2H, bs), 7.35 (2H, d, J=9.4 Hz), 7.38 (1H, d, J=2.0 Hz), 7.68 (1H, d, J=2.0, 8.6 Hz), 8.26 (2H, d, J=9.4 Hz), 8.34 (1H, d, J=8.6 Hz), 8.83 (3H, bs).

35 Example 16

3-(Aminomethyl)-6-chloro-4-(4-methoxyphenyl)-2-methyl-1(2H)-isoquinolinone hydrochloride

(1) To a solution of ethyl 6-chloro-4-hydroxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 5 (1)) (8.45 g, 30 mmol) in tetrahydrofuran (100 ml) was added sodium hydride (1.44 g, 36 mmol) (60% in oil) at 0°C and the mixture was stirred at 0°C for 30 min. To the obtained mixture was added N-phenyltrifluoromethane sulfonimide (12.86 g, 36 mmol) and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give ethyl 6-chloro-2-methyl-1-oxo-4-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinecarboxylate (8.54 g, 68.8%) as crystals.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.45 (3H, t, J=7.0 Hz), 3.60 (3H, s), 4.49 (2H, q, J=7.0 Hz), 7.60 (1H, dd, J=2.0, 8.6 Hz), 7.75 (1H, d, J=2.0 Hz), 8.40 (1H, d, J=8.6 Hz).

(2) Ethyl 6-chloro-4-(4-methoxyphenyl)-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 12 (2))

Melting point 135-136°C.

Elemental analysis for C<sub>20</sub>H<sub>18</sub>NO<sub>4</sub>Cl

Calculated: C, 64.61; H, 4.88; N, 3.77.

Found: C, 64.81; H, 4.87; N, 3.57.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.00 (3H, t, J=7.2 Hz), 3.59 (3H, s), 3.88 (3H, s), 4.07 (2H, q, J=7.2 Hz), 6.98 (2H, d, J=8.8 Hz), 7.232 (2H, d, J=8.8 Hz), 7.24 (1H, d, J=2.0 Hz), 7.47 (1H, d, J=2.0, 8.6 Hz), 8.34 (1H, d, J=8.6 Hz).

(3) 6-Chloro-4-(4-methoxyphenyl)-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized

according to the method similar to that in Example 4 (3))

Melting point 242-243°C.

Elemental analysis for  $C_{18}H_{14}NO_4Cl$

5 Calculated: C, 62.89; H, 4.10; N, 4.07.

Found: C, 63.06; H, 4.18; N, 4.01.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 3.52 (3H, s), 3.83 (3H, s), 7.04 (1H, d, J=2.2 Hz), 7.06 (2H, d, J=8.6 Hz), 7.26 (2H, d, J=8.6 Hz), 7.62 (1H, d, J=2.2, 8.6 Hz), 8.32 (1H, d, J=8.6 Hz)..

10 (4) 6-Chloro-4-(4-methoxyphenyl)-3-hydroxymethyl-2-methyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

Melting point 187-188°C.

Elemental analysis for  $C_{18}H_{16}NO_3Cl$

15 Calculated: C, 65.56; H, 4.89; N, 4.25.

Found: C, 65.62; H, 5.04; N, 4.09.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 2.26 (1H, bs), 3.80 (3H, s), 3.90 (3H, s), 4.47 (2H, d, J=5.6 Hz), 7.01-7.06 (3H, m), 7.18-7.25 (3H, m), 7.35 (1H, dd, J=1.8, 8.6 Hz), 8.33 (1H, d, J=8.6 Hz).

20 (5) 6-Chloro-3-chloromethyl-4-(4-methoxyphenyl)-2-methyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 3.82 (3H, s), 3.91 (3H, s), 4.41 (2H, s), 25 7.03-7.08 (3H, m), 7.24 (2H, d, J=8.0 Hz), 7.43 (1H, dd, J=2.0, 8.6 Hz), 8.42 (1H, d, J=8.6 Hz).

(6) 2-((6-Chloro-4-(4-methoxyphenyl)-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to 30 that in Example 4 (6))

Melting point 207-208°C.

Elemental analysis for  $C_{26}H_{19}N_2O_4Cl$

Calculated: C, 68.05; H, 4.17; N, 6.10.

Found: C, 68.24; H, 4.25; N, 5.96.

35  $^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 3.58 (3H, s), 3.77 (3H, s), 4.77 (2H, s), 6.83 (1H, d, J=2.0 Hz), 6.98 (2H, d, J=8.8 Hz), 7.20



(2H, d, J=8.8 Hz), 7.55 (1H, dd, J=2.0, 8.6 Hz), 7.75-7.85 (4H, m), 8.29 (1H, d, J=8.6 Hz).

(7) Tert-butyl {6-chloro-4-(4-methoxyphenyl)-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl}methylcarbamate

5 (synthesized according to the method similar to that in Example 1 (6))

Melting point 187-188°C.

Elemental analysis for  $C_{23}H_{25}N_2O_4Cl$

Calculated: C, 64.41; H, 5.88; N, 6.53.

10 Found: C, 64.72; H, 5.96; N, 6.51.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.43 (9H, s), 3.69 (3H, s), 3.91 (3H, s), 4.21 (2H, d, J=5.8 Hz), 4.65 (1H, bs), 6.95 (1H, d, J=2.0 Hz), 7.02 (2H, d, J=8.9 Hz), 7.15 (2H, d, J=8.9 Hz), 7.36 (1H, dd, J=2.0, 8.6 Hz), 8.35 (1H, d, J=8.6

15 Hz).

(8) 3-(Aminomethyl)-6-chloro-4-(4-methoxyphenyl)-2-methyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

20 Melting point 249-250°C.

Elemental analysis for  $C_{18}H_{18}N_2O_2Cl_2$

Calculated: C, 59.19; H, 4.97; N, 7.67.

Found: C, 59.23; H, 4.81; N, 7.30.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 3.71 (3H, s), 3.87 (3H, s), 3.95 (2H, bs), 6.88 (1H, d, J=2.0 Hz), 7.14 (2H, d, J=8.8 Hz), 7.32 (2H, d, J=8.8 Hz), 7.62 (1H, dd, J=2.0, 8.6 Hz), 8.33 (1H, d, J=8.6 Hz), 8.66 (3H, bs).

25

#### Example 17

3-(Aminomethyl)-6-chloro-4-(3-methoxyphenyl)-2-methyl-1(2H)-isoquinolinone hydrochloride

30

(1) Ethyl 6-chloro-4-(3-methoxyphenyl)-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 12 (2))

35

Melting point 146-147°C.

Elemental analysis for  $C_{20}H_{18}NO_4Cl$

Calculated: C, 64.61; H, 4.88; N, 3.77.

Found: C, 64.55; H, 4.84; N, 3.69.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.97 (3H, t,  $J=7.2$  Hz), 3.60 (3H, s),  
3.83 (3H, s), 4.06 (2H, q,  $J=7.2$  Hz), 6.84-7.09 (3H, m),  
5 7.23 (1H, d,  $J=2.0$  Hz), 7.37 (1H, t,  $J=7.9$  Hz), 7.47 (1H,  
dd,  $J=2.0$ , 8.6 Hz), 8.44 (1H, d,  $J=8.6$  Hz).

(2) 6-Chloro-4-(3-methoxyphenyl)-2-methyl-1-oxo-1,2-  
dihydro-3-isoquinolinecarboxylic acid (synthesized  
according to the method similar to that in Example 4

10 (3))

Melting point 212-213°C.

Elemental analysis for  $\text{C}_{18}\text{H}_{14}\text{NO}_4\text{Cl}$

Calculated: C, 62.89; H, 4.10; N, 4.07.

Found: C, 63.14; H, 4.22; N, 3.90.

15  $^1\text{H-NMR}(\text{DMSO}-d_6)$   $\delta$ : 3.52 (3H, s), 3.78 (3H, s), 6.90-6.94  
(2H, m), 7.03-7.07 (2H, m), 7.44 (1H, t,  $J=8.1$  Hz), 7.62  
(1H, dd,  $J=2.0$ , 8.6 Hz), 8.32 (1H, d,  $J=8.6$  Hz)

(3) 6-Chloro-4-(3-methoxyphenyl)-3-hydroxymethyl-2-  
methyl-1(2H)-isoquinolinone (synthesized according to  
20 the method similar to that in Example 4 (4))

Melting point 127-128°C.

Elemental analysis for  $\text{C}_{18}\text{H}_{16}\text{NO}_3\text{Cl}$

Calculated: C, 65.56; H, 4.89; N, 4.25.

Found: C, 65.72; H, 5.14; N, 4.04.

25  $^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 2.00 (1H, bs), 3.81 (3H, s), 3.86 (3H, s),  
4.47 (2H, s), 6.82-6.89 (2H, m), 6.99-7.04 (2H, m), 7.38  
(1H, dd,  $J=2.1$ , 8.6 Hz), 7.43 (1H, t,  $J=7.9$  Hz), 8.37  
(1H, d,  $J=8.6$  Hz).

(4) 6-Chloro-3-chloromethyl-4-(3-methoxyphenyl)-2-  
30 methyl-1(2H)-isoquinolinone (synthesized according to  
the method similar to that in Example 4 (5))

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 3.82 (3H, s), 3.86 (3H, s), 4.40 (2H, s),  
6.88-6.92 (1H, m), 7.01-7.07 (2H, m), 7.44 (1H, dd,  
 $J=2.0$ , 8.6 Hz), 7.45 (1H, t,  $J=8.0$  Hz), 8.42 (1H, d,  
35  $J=8.6$  Hz).

(5) 2-((6-Chloro-4-(3-methoxyphenyl)-2-methyl-1-oxo-1,2-

dihydro-3-isoquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 184-185°C.

5 Elemental analysis for  $C_{26}H_{19}N_2O_4Cl$

Calculated: C, 68.05; H, 4.17; N, 6.10.

Found: C, 67.69; H, 4.40; N, 5.82.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 3.61 (3H, s), 3.63 (3H, s), 4.78 (2H, s), 6.08-6.84 (3H, m), 6.90-6.95 (1H, m), 7.33 (1H, t,  $J=8.1$  Hz), 7.55 (1H, dd,  $J=2.0, 8.6$  Hz), 7.74-7.84 (4H, m), 8.30 (1H, d,  $J=8.6$  Hz).

(6) Tert-butyl {6-chloro-4-(3-methoxyphenyl)-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate

(synthesized according to the method similar to that in

15 Example 1 (6)).

Melting point 231-232°C.

Elemental analysis for  $C_{23}H_{25}N_2O_4Cl$

Calculated: C, 64.41; H, 5.88; N, 6.53.

Found: C, 64.25; H, 5.49; N, 6.34.

20  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.43 (9H, s), 3.70 (3H, s), 3.86 (3H, s), 4.21-4.23 (2H, m), 4.60 (1H, bs), 6.77-6.84 (2H, m), 6.96 (1H, d,  $J=1.8$  Hz), 6.99-7.05 (1H, m), 7.35-7.48 (2H, m), 8.37 (1H, d,  $J=8.8$  Hz).

(7) 3-(Aminomethyl)-6-chloro-4-(3-methoxyphenyl)-2-methyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1

(7)).

Melting point 237-238°C.

Elemental analysis for  $C_{18}H_{18}N_2O_2Cl_2 \cdot 1/2H_2O$

30 Calculated: C, 57.77; H, 5.12; N, 7.67.

Found: C, 57.62; H, 5.23; N, 7.40.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 3.71 (3H, s), 3.82 (3H, s), 3.92-3.98 (2H, m), 6.87 (1H, d,  $J=2.0$  Hz), 6.94 (1H, d,  $J=7.5$  Hz), 7.01 (1H, bs), 7.11 (1H, dd,  $J=2.6, 8.1$  Hz), 7.51 (1H, dd,  $J=7.5, 8.1$  Hz), 7.62 (1H, dd,  $J=2.0, 8.6$  Hz), 8.33 (1H, d,  $J=8.6$  Hz), 8.63 (3H, bs).

**Example 18**

3-(Aminomethyl)-6-chloro-4-(4-hydroxyphenyl)-2-methyl-1(2H)-isoquinolinone hydrochloride

- (1) To a solution of 2-([6-chloro-4-(4-methoxyphenyl)-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methyl)-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 16 (7)). (0.92 g, 2 mmol) in dichloromethane (10 ml) was added boron tribromide (0.76 ml, 36 mmol) at 0°C and the mixture was stirred at 0°C for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from tetrahydrofuran - diisopropyl ether to give 2-([6-chloro-4-(4-hydroxyphenyl)-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methyl)-1H-isoindole-1,3(2H)-dione (0.83 g, 94.3%) as crystals.

Melting point 307-308°C.

- (2) Elemental analysis for  $C_{25}H_{17}N_2O_4Cl \cdot H_2O$ .

Calculated: C, 64.87; H, 4.14; N, 6.05.

Found: C, 64.44; H, 3.88; N, 5.66.

- $^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 3.67 (3H, s), 4.76 (2H, s), 6.81 (2H, d, J=8.6 Hz), 6.86 (1H, d, J=2.0 Hz), 7.08 (2H, d, J=8.6 Hz), 7.54 (1H, dd, J=2.0, 8.6 Hz), 7.75-7.85 (4H, m), 8.28 (1H, d, J=8.6 Hz), 9.60 (1H, s).

- (2) Tert-butyl 4-{3-[(tert-butoxycarbonyl)amino]methyl}-6-chloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl}phenylcarbonate (synthesized according to the method similar to that in Example 1 (6))

Melting point 195-196°C.

Elemental analysis for  $C_{27}H_{31}N_2O_6Cl$

Calculated: C, 62.97; H, 6.07; N, 5.44.

- Found: C, 63.02; H, 6.28; N, 5.34.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.41 (9H, s), 1.61 (9H, s), 3.69 (3H, s),

4.20 (2H, d, J=6.0 Hz), 4.62 (1H, bs), 6.92 (1H, d, J=1.8 Hz), 7.24-7.40 (5H, m), 8.35 (1H, d, J=8.6 Hz).

(3) 3-(Aminomethyl)-6-chloro-4-(4-hydroxyphenyl)-2-methyl-1(2H)-isoquinolinone hydrochloride (synthesized

5 according to the method similar to that in Example 1 (7))

Melting point 253-254°C.

Elemental analysis for  $C_{17}H_{16}N_2O_2Cl_2$

Calculated: C, 58.13; H, 4.59; N, 7.98.

10 Found: C, 57.99; H, 4.57; N, 7.88.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 3.70 (3H, s), 3.97 (2H, bs), 6.92 (1H, d, J=2.0 Hz), 6.97 (2H, d, J=8.4 Hz), 7.17 (2H, d, J=8.4 Hz), 7.60 (1H, dd, J=2.0, 8.6 Hz), 8.32 (1H, d, J=8.6 Hz), 8.62 (3H, bs), 9.89 (1H, bs).

15 **Example 19**

3-(Aminomethyl)-6-chloro-4-(3-hydroxyphenyl)-2-methyl-1(2H)-isoquinolinone hydrochloride

(1) 2-([6-Chloro-4-(3-hydroxyphenyl)-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methyl)-1H-isoindole-1,3(2H)-

20 dione (synthesized according to the method similar to that in Example 18 (1))

Melting point 297-298°C.

Elemental analysis for  $C_{25}H_{17}N_2O_4Cl \cdot 1/4H_2O$

Calculated: C, 66.82; H, 4.00; N, 6.23.

25 Found: C, 66.52; H, 4.34; N, 5.85.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 3.58 (3H, s), 4.73 (1H, d, J=15.8 Hz), 4.82 (1H, d, J=15.8 Hz), 6.65-6.70 (2H, m), 6.76-6.80 (1H, m), 6.85 (1H, d, J=2.0 Hz), 7.20 (1H, t, J=7.7 Hz), 7.55 (1H, dd, J=2.0, 8.6 Hz), 7.75-7.85 (4H, m), 8.29

30 (1H, d, J=8.6 Hz), 9.57 (1H, s).

(2) Tert-butyl {6-chloro-4-(3-hydroxyphenyl)-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl}methylcarbamate

(synthesized according to the method similar to that in Example 1 (6))

35 Melting point 244-245°C.

Elemental analysis for  $C_{22}H_{23}N_2O_4Cl$

Calculated: C, 63.69; H, 5.59; N, 6.75.

Found: C, 63.76; H, 5.75; N, 6.52.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:1.44 (9H, s), 3.69 (3H, s), 4.23 (2H, d, J=5.6 Hz), 4.86 (1H, bs), 6.69-6.75 (2H, m), 6.95-7.00 (1H, m), 7.02 (1H, d, J=2.0 Hz), 7.33 (1H, t, J=7.7 Hz), 7.37 (1H, dd, J=2.0, 8.6 Hz), 8.36 (1H, d, J=8.6 Hz), 8.87 (1H, s).

(3) 3-(Aminomethyl)-6-chloro-4-(3-hydroxyphenyl)-2-methyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7)).

Melting point 277°C.

Elemental analysis for C<sub>17</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>Cl<sub>2</sub>

Calculated: C, 58.13; H, 4.59; N, 7.98.

Found: C, 57.96; H, 4.66; N, 8.01.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ:3.69 (3H, s), 3.97 (2H, bs), 6.78-6.81 (2H, m), 6.90 (1H, d, J=2.0 Hz), 6.94-6.99 (1H, m), 7.38 (1H, t, J=7.9 Hz), 7.62 (1H, dd, J=2.0, 8.6 Hz), 8.32 (1H, d, J=8.6 Hz), 8.60 (3H, bs), 9.87 (1H, bs).

#### Example 20

3-(Aminomethyl)-6-chloro-4-(4-fluorophenyl)-2-methyl-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 6-chloro-4-(4-fluorophenyl)-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized

according to the method similar to that in Example 12 (2))

Melting point 159-160°C.

Elemental analysis for C<sub>19</sub>H<sub>15</sub>NO<sub>3</sub>ClF

Calculated: C, 63.43; H, 4.20; N, 3.89.

Found: C, 63.56; H, 3.96; N, 3.66.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:1.00 (3H, t, J=7.0 Hz), 3.59 (3H, s), 4.07 (2H, q, J=7.0 Hz), 7.12 (1H, d, J=2.0 Hz), 7.17-7.21 (2H, m), 7.27-7.347 (2H, m), 7.48 (1H, dd, J=2.0, 8.6 Hz), 8.44 (1H, d, J=8.6 Hz).

(2) 6-Chloro-4-(4-fluorophenyl)-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized

according to the method similar to that in Example 4  
(3))

Melting point 239-240°C.

Elemental analysis for  $C_{17}H_{11}NO_3ClF$

5 Calculated: C, 61.55; H, 3.34; N, 4.22.

Found: C, 61.82; H, 3.52; N, 4.02.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 3.52 (3H, s), 6.99 (1H, d,  $J=2.0$  Hz),  
7.30-7.45 (4H, m), 7.63 (1H, dd,  $J=2.0, 8.6$  Hz), 8.33  
(1H, d,  $J=8.6$  Hz).

10 (3) 6-Chloro-4-(4-fluorophenyl)-3-hydroxymethyl-2-  
methyl-1(2H)-isoquinolinone (synthesized according to  
the method similar to that in Example 4 (4))

Melting point 167-168°C.

Elemental analysis for  $C_{17}H_{13}NO_2ClF$

15 Calculated: C, 64.26; H, 4.12; N, 4.41.

Found: C, 64.33; H, 4.08; N, 4.36.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 2.08 (1H, bs), 3.81 (3H, s), 4.45 (2H, d,  
 $J=5.2$  Hz), 6.94 (1H, d,  $J=2.0$  Hz), 7.17-7.33 (4H, m),  
7.38 (1H, d,  $J=2.0, 8.6$  Hz), 8.36 (1H, d,  $J=8.6$  Hz).

20 (4) 6-Chloro-3-chloromethyl-4-(4-fluorophenyl)-2-methyl-  
1(2H)-isoquinolinone (synthesized according to the  
method similar to that in Example 4 (5))

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 3.82 (3H, s), 4.37 (2H, s), 6.97 (1H, d,  
 $J=2.0$  Hz), 7.20-7.37 (4H, m), 7.45 (1H, dd,  $J=2.0, 8.6$   
25 Hz), 8.43 (1H, d,  $J=8.6$  Hz).

(5) 2-([6-Chloro-4-(4-fluorophenyl)-2-methyl-1-oxo-1,2-  
dihydro-3-isoquinolinyl]methyl)-1H-isoindole-1,3(2H)-  
dione (synthesized according to the method similar to  
that in Example 4 (6))

30 Melting point 190-191°C.

Elemental analysis for  $C_{25}H_{16}N_2O_3ClF$

Calculated: C, 67.20; H, 3.61; N, 6.27.

Found: C, 67.40; H, 3.42; N, 6.24.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 3.61 (3H, s), 4.75 (2H, s), 6.78 (1H,  
35 d,  $J=2.0$  Hz), 7.23-7.39 (4H, m), 7.57 (1H, dd,  $J=2.0,$   
8.6 Hz), 7.76-7.85 (4H, m), 7.86 (4H, s), 8.31 (1H, d,

J=8.6 Hz).

(6) Tert-butyl {6-chloro-4-(4-fluorophenyl)-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl}methylcarbamate  
(synthesized according to the method similar to that in

5 Example 1 (6))

Melting point 206-207°C.

Elemental analysis for  $C_{22}H_{22}N_2O_3ClF$

Calculated: C, 63.39; H, 5.32; N, 6.72.

Found: C, 63.56; H, 5.27; N, 6.61.

10  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.44 (9H, s), 3.69 (3H, s), 4.19 (2H, d, J=5.6 Hz), 4.67 (1H, bs), 6.88 (1H, d, J=2.0 Hz), 7.22-7.27 (4H, m), 7.38 (1H, dd, J=2.0, 8.6 Hz), 8.35 (1H, d, J=8.6 Hz).

(7) 3-(Aminomethyl)-6-chloro-4-(4-fluorophenyl)-2-methyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 277-278°C.

Elemental analysis for  $C_{17}H_{15}N_2OCl_2F$

20 Calculated: C, 57.81; H, 4.28; N, 7.93.

Found: C, 57.98; H, 4.29; N, 7.84.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 3.71 (3H, s), 3.92 (2H, s), 6.83 (1H, d, J=2.0 Hz), 7.37-7.46 (4H, m), 7.62 (1H, dd, J=2.0, 8.6 Hz), 8.34 (1H, d, J=8.6 Hz), 8.73 (3H, bs).

25 Example 21

3-(Aminomethyl)-6-chloro-2-methyl-4-(4-trifluoromethylphenyl)-1(2H)-isoquinolinone hydrochloride

(1) 6-Chloro-2-methyl-1-oxo-4-(4-trifluoromethylphenyl)-1,2-dihydro-3-isoquinolinecarboxylate ethyl (synthesized according to the method similar to that in Example 12 (2))

Melting point 170-171°C.

Elemental analysis for  $C_{20}H_{15}NO_3ClF_3$

35 Calculated: C, 58.62; H, 3.69; N, 3.40.

Found: C, 58.83; H, 3.71; N, 3.22.



<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.93 (3H, t, J=7.2 Hz), 3.60 (3H, s), 4.05 (2H, q, J=7.2 Hz), 7.09 (1H, d, J=2.0 Hz), 7.46 (2H, d, J=7.8 Hz), 7.50 (1H, dd, J=2.0, 8.4 Hz), 7.75 (2H, d, J=7.8 Hz), 8.46 (1H, d, J=8.4 Hz).

- 5 (2) 6-Chloro-2-methyl-1-oxo-4-(4-trifluoromethylphenyl)-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 285-286°C.

- 10 Elemental analysis for C<sub>18</sub>H<sub>11</sub>NO<sub>3</sub>ClF<sub>3</sub>

Calculated: C, 56.63; H, 2.90; N, 3.67.

Found: C, 56.73; H, 2.68; N, 3.49.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ:3.53 (3H, s), 6.99 (1H, d, J=2.2 Hz), 7.60 (2H, d, J=8.0 Hz), 7.65 (1H, dd, J=2.2, 8.4 Hz), 7.89 (2H, d, J=8.0 Hz), 8.34 (1H, d, J=8.4 Hz).

- 15 (3) 6-Chloro-3-hydroxymethyl-2-methyl-4-(4-trifluoromethylphenyl)-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

- 20 Melting point 219-220°C.

Elemental analysis for C<sub>18</sub>H<sub>13</sub>NO<sub>2</sub>ClF<sub>3</sub>

Calculated: C, 58.79; H, 3.56; N, 3.81.

Found: C, 58.94; H, 3.52; N, 3.65.

- <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:2.13 (1H, bs), 3.82 (3H, s), 4.43 (2H, d, J=5.0 Hz), 7.40 (1H, dd, J=2.0, 8.6 Hz), 7.47 (2H, d, J=7.9 Hz), 7.80 (2H, d, J=7.9 Hz), 8.37 (1H, d, J=8.6 Hz).

- (4) 6-Chloro-3-chloromethyl-2-methyl-4-(4-trifluoromethylphenyl)-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

- <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:3.83 (3H, s), 4.33 (2H, s), 6.91 (1H, d, J=1.8 Hz), 7.47 (1H, dd, J=1.8, 8.6 Hz), 7.50 (2H, d, J=7.5 Hz), 7.83 (2H, d, J=7.5 Hz), 8.45 (1H, d, J=8.6 Hz).

- 35 (5) 2-((6-Chloro-2-methyl-1-oxo-4-(4-

trifluoromethylphenyl)-1,2-dihydro-3-  
isoquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione  
(synthesized according to the method similar to that in  
Example 4 (6)).

5 Melting point 236-237°C.

Elemental analysis for  $C_{26}H_{16}N_2O_3ClF_3$

Calculated: C, 62.85; H, 3.25; N, 5.64.

Found: C, 62.92; H, 3.07; N, 5.52.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 3.62 (3H, s), 4.76 (2H, s), 6.73 (1H,  
10 d, J=1.8 Hz), 7.54 (2H, d, J=7.6 Hz), 7.58 (1H, dd,  
J=1.8, 8.4 Hz), 7.73-7.84 (6H, m), 8.32 (1H, d, J=8.4  
Hz).

(6) Tert-butyl {6-chloro-2-methyl-1-oxo-4-(4-  
trifluoromethylphenyl)-1,2-dihydro-3-isoquinolinyl}-

15 methylcarbamate (synthesized according to the method  
similar to that in Example 1 (6))

Melting point 193-194°C.

Elemental analysis for  $C_{23}H_{22}N_2O_3ClF_3$

Calculated: C, 59.17; H, 4.75; N, 6.00.

20 Found: C, 59.35; H, 4.76; N, 5.92.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.43 (9H, s), 3.70 (3H, s), 4.16 (2H, d,  
J=5.8 Hz), 4.67 (1H, bs), 6.82 (1H, d, J=2.0 Hz), 7.39  
(1H, dd, J=2.0, 8.6 Hz), 7.42 (2H, d, J=7.9 Hz), 7.81  
(2H, d, J=7.9 Hz), 8.36 (1H, d, J=8.6 Hz).

25 (7) 3-(Aminomethyl)-6-chloro-2-methyl-4-(4-  
trifluoromethylphenyl)-1(2H)-isoquinolinone  
hydrochloride (synthesized according to the method  
similar to that in Example 1 (7))

Melting point 261-262°C.

30 Elemental analysis for  $C_{18}H_{15}N_2OCl_2F_3 \cdot 1/2H_2O$

Calculated: C, 52.44; H, 3.91; N, 6.80.

Found: C, 52.57; H, 4.09; N, 7.02.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 3.71 (3H, s), 3.90 (2H, s), 6.79 (1H,  
d, J=2.0 Hz), 7.64 (1H, dd, J=2.0, 8.8 Hz), 7.65 (2H, d,  
35 J=8.2 Hz), 7.96 (2H, d, J=8.2 Hz), 8.35 (1H, d, J=8.8  
Hz), 8.70 (3H, bs).

**Example 22**

3-(Aminomethyl)-6,7-dichloro-2-methyl-4-phenyl-1(2H)-isoquinolinone hydrochloride

- 5 (1) ethyl 6,7-dichloro-4-hydroxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 4 (1))

Melting point 127-128°C.

Elemental analysis for  $C_{13}H_{11}NO_4Cl_2$

Calculated: C, 49.39; H, 3.51; N, 4.43.

- 10 Found: C, 49.31; H, 3.50; N, 4.36.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.47 (3H, t, J=7.2 Hz), 3.68 (3H, s), 4.51 (2H, q, J=7.2 Hz), 8.21 (1H, s), 8.51 (1H, bs), 11.17 (1H, s).

- 15 (2) Ethyl 6,7-dichloro-2-methyl-1-oxo-4-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 12 (1))

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.45 (3H, t, J=7.2 Hz), 3.60 (3H, s), 4.49 (2H, q, J=7.2 Hz), 7.86 (1H, s), 8.53 (1H, s).

- 20 (3) Ethyl 6,7-dichloro-2-methyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 12 (2))

Melting point 288-289°C.

Elemental analysis for  $C_{19}H_{15}NO_3Cl_2$

- 25 Calculated: C, 60.65; H, 4.02; N, 3.72.

Found: C, 60.96; H, 4.04; N, 3.62.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.92 (3H, t, J=7.2 Hz), 3.60 (3H, s), 4.02 (2H, q, J=7.2 Hz), 7.28-7.32 (3H, m), 7.45-7.48 (3H, m), 8.57 (1H, s).

- 30 (4) 6,7-Dichloro-2-methyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 261-262°C.

- 35  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 3.68 (3H, s), 7.13 (1H, d, J=8.8 Hz), 7.32-7.51 (6H, m), 8.45 (1H, d, J=2.2 Hz).

(5) 6,7-Dichloro-3-hydroxymethyl-2-methyl-4-phenyl-

1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

Melting point 211-212°C.

Elemental analysis for  $C_{17}H_{13}NO_2Cl_2$

5 Calculated: C, 61.10; H, 3.92; N, 4.19.

Found: C, 61.21; H, 3.80; N, 4.12.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 2.22 (1H, t,  $J=5.8$  Hz), 3.81 (3H, s), 4.45 (2H, d,  $J=5.8$  Hz), 7.09 (1H, s), 7.27-7.33 (2H, m), 7.48-7.56 (3H, m), 8.47 (1H, s).

10 (6) 6,7-Dichloro-3-chloromethyl-2-methyl-4-phenyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 3.82 (3H, s), 4.36 (2H, s), 7.11 (1H, s), 7.31-7.34 (2H, m), 7.49-7.56 (3H, m), 8.57 (1H, s).

15 (7) 2-((6,7-Dichloro-2-methyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 234-235°C.

20 Elemental analysis for  $C_{25}H_{16}N_2O_3Cl_2$

Calculated: C, 64.81; H, 3.48; N, 6.05.

Found: C, 64.68; H, 3.56; N, 5.86.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 3.61 (3H, s), 4.76 (2H, s), 6.94 (1H, s), 7.28-7.32 (2H, m), 7.41-7.48 (3H, m), 8.40 (1H, s).

25 (8) Tert-butyl {6,7-dichloro-2-methyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl}methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

Melting point 226-227°C.

30 Elemental analysis for  $C_{22}H_{22}N_2O_3Cl_2$

Calculated: C, 60.98; H, 5.12; N, 6.46.

Found: C, 61.10; H, 5.30; N, 6.37.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.43 (9H, s), 3.70 (3H, s), 4.19 (2H, d,  $J=5.4$  Hz), 4.77 (1H, bs), 7.02 (1H, s), 7.22-7.27 (2H, m), 7.49-7.53 (3H, m), 8.47 (1H, s).

(9) 3-(Aminomethyl)-6,7-dichloro-2-methyl-4-phenyl-

1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 4 (7))

Melting point 266-267°C.

5 Elemental analysis for  $C_{17}H_{15}N_2OCl_3$

Calculated: C, 55.23; H, 4.09; N, 7.58.

Found: C, 55.40; H, 4.21; N, 7.33.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 3.72 (3H, s), 3.93 (2H, bs), 6.99 (1H, s), 7.39-7.44 (2H, m), 7.55-7.64 (3H, m), 8.43 (1H, s), 8.73 (3H, bs).

#### Example 23

3-(Aminomethyl)-6-chloro-2-methyl-4-(3-nitrophenyl)-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 6-chloro-2-methyl-1-oxo-4-(3-nitrophenyl)-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 12 (2))

Melting point 211-212°C.

Elemental analysis for  $C_{19}H_{15}N_2O_5Cl$

Calculated: C, 59.00; H, 3.91; N, 7.24.

20 Found: C, 59.13; H, 3.86; N, 7.32.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.02 (3H, t,  $J=7.2$  Hz), 3.61 (3H, s), 4.09 (2H, q,  $J=7.2$  Hz), 7.02 (1H, d,  $J=2.0$  Hz), 7.52 (1H, dd,  $J=2.0, 8.6$  Hz), 7.68-7.71 (2H, m), 8.23-8.25 (1H, m), 8.32-8.38 (1H, m), 8.47 (1H, d,  $J=8.6$  Hz).

25 (2) 6-Chloro-2-methyl-1-oxo-4-(3-nitrophenyl)-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 259-260°C.

30  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 3.54 (3H, s), 7.04 (1H, d,  $J=2.0$  Hz), 7.65 (1H, dd,  $J=2.0, 8.6$  Hz), 7.82-7.85 (2H, m), 8.19-8.21 (1H, m), 8.33-8.39 (2H, m).

(3) 6-Chloro-3-hydroxymethyl-2-methyl-4-(3-nitrophenyl)-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

35 Melting point 227-228°C.

Elemental analysis for  $C_{17}H_{13}N_2O_4Cl \cdot 1/2H_2O$

Calculated: C, 57.72; H, 3.99; N, 7.92.

Found: C, 57.96; H, 3.88; N, 7.63.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 3.85 (3H, s), 4.34 (2H, d,  $J=3.2$  Hz),  
5 4.80 (1H, bs), 6.86 (1H, d,  $J=2.0$  Hz), 7.42 (1H, dd,  
 $J=2.0, 8.6$  Hz), 7.69-7.73 (2H, m), 8.27-8.38 (2H, m),  
8.43 (1H, d,  $J=8.6$  Hz).

(4) 6-Chloro-3-chloromethyl-2-methyl-4-(3-nitrophenyl)-  
1(2H)-isoquinolinone (synthesized according to the  
10 method similar to that in Example 4 (5))

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 3.84 (3H, s), 4.32 (2H, s), 6.86 (1H, d,  
 $J=2.0$  Hz), 7.49 (1H, dd,  $J=2.0, 8.6$  Hz), 7.73-7.79 (2H,  
m), 8.25-8.26 (1H, m), 8.39-8.43 (1H, m), 8.46 (1H, d,  
 $J=8.6$  Hz).

15 (5) 2-((6-Chloro-2-methyl-1-oxo-4-(3-nitrophenyl)-1,2-  
dihydro-3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-  
dione (synthesized according to the method similar to  
that in Example 4 (6))

Melting point 246-247°C.

20 Elemental analysis for  $C_{25}H_{16}N_3O_5Cl$

Calculated: C, 63.37; H, 3.40; N, 8.87.

Found: C, 63.14; H, 3.33; N, 8.50.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 3.65 (3H, s), 4.71 (1H, d,  $J=16.3$  Hz),  
4.80 (1H, d,  $J=16.3$  Hz), 6.79 (1H, d,  $J=2.0$  Hz), 7.59  
25 (1H, d,  $J=2.0, 8.6$  Hz), 7.69-7.84 (5H, m), 8.13-8.14 (1H,  
m), 8.23-8.29 (4H, m), 8.33 (1H, d,  $J=8.6$  Hz).

(6) Tert-butyl {6-chloro-2-methyl-1-oxo-4-(3-  
nitrophenyl)-1,2-dihydro-3-isoquinolinyl}methylcarbamate  
(synthesized according to the method similar to that in  
30 Example 1 (6))

Melting point 231-232°C.

Elemental analysis for  $C_{22}H_{22}N_3O_5Cl$

Calculated: C, 59.53; H, 5.00; N, 9.47.

Found: C, 59.51; H, 5.01; N, 9.25.

35  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.42 (9H, s), 3.71 (3H, s), 4.14-4.17  
(2H, m), 4.81 (1H, bs), 6.77 (1H, s), 7.18-7.23 (1H, m),

7.62 (1H, d, J=7.8 Hz), 7.76 (1H, t, J=7.8 Hz), 8.17 (1H, s), 8.36-8.42 (2H, m).

(7) 3-(Aminomethyl)-6-chloro-2-methyl-4-(3-nitrophenyl)-1(2H)-isoquinolinone hydrochloride (synthesized

5 according to the method similar to that in Example 1 (7))

Melting point 263-264°C.

Elemental analysis for  $C_{17}H_{15}N_3O_3Cl_2$

Calculated: C, 53.70; H, 3.98; N, 11.05.

10 Found: C, 53.56; H, 4.09; N, 10.95.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 3.71 (3H, s), 3.83-3.93 (2H, m), 3.686 (1H, d, J=2.0 Hz), 7.65 (1H, dd, J=2.0, 8.6 Hz), 7.82-7.93 (2H, m), 8.23-8.25 (1H, m), 8.35 (1H, d, J=8.6 Hz), 8.39-8.44 (1H, m), 8.66 (3H, bs).

15 **Example 24**

3-(Aminomethyl)-4-(3-aminophenyl)-6-chloro-2-methyl-1(2H)-isoquinolinone hydrochloride

(1) Tert-butyl {6-chloro-2-methyl-1-oxo-4-(3-nitrophenyl)-1,2-dihydro-3-isoquinolinyl}methylcarbamate  
20 (synthesized according to the method similar to that in Example 23 (6)) (0.89 g, 2 mmol) was added to an aqueous solution (10 ml) of potassium carbonate (2.90 g, 21 mmol) and sodium hydrosulfite (2.44 g, 14 mmol) and the mixture was stirred at room temperature for 1 h. The  
25 reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography  
30 to give tert-butyl {4-(3-aminophenyl)-6-chloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.48 g, 58.5%) as crystals.

Melting point 157-158°C.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.43 (9H, s), 3.69 (3H, s), 4.22 (2H, d, J=5.6 Hz), 4.65 (1H, bs), 6.54-6.62 (1H, m), 6.76-6.83 (1H, m), 6.90-7.03 (1H, m), 7.08 (1H, dd, J=2.0, 8.0 Hz),

7.34-7.45 (2H, m), 8.35 (1H, d, J=8.0 Hz).

(2) 3-(Aminomethyl)-4-(3-aminophenyl)-6-chloro-2-methyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1

5 (7))

Melting point 255°C.

Elemental analysis for  $C_{17}H_{18}N_3OCl_3 \cdot 1/2H_2O$

Calculated: C, 51.60; H, 4.84; N, 10.62.

Found: C, 51.76; H, 4.64; N, 10.29.

10  $^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 3.70 (3H, s), 3.91 (2H, bs), 6.87-6.93 (2H, m), 7.38-7.46 (1H, m), 7.57-7.75 (3H, m), 8.35 (1H, d, J=8.8 Hz), 8.73-8.87 (6H, m).

#### Example 25

15 3-(Aminomethyl)-4-butoxy-6-chloro-2-propyl-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 6-chloro-4-hydroxy-1-oxo-2-propyl-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (1))

Melting point 61-62°C.

20 Elemental analysis for  $C_{15}H_{16}NO_4Cl$

Calculated: C, 58.16; H, 5.21; N, 4.52.

Found: C, 58.22; H, 5.28; N, 4.45.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.93 (3H, t, J=7.3 Hz), 1.47 (3H, t, J=7.2 Hz), 1.69-1.84 (2H, m), 4.17-4.24 (2H, m), 4.51 (2H, q, J=7.2 Hz), 7.62 (1H, dd, J=2.2, 8.6 Hz), 8.11 (1H, d, J=2.2 Hz), 8.37 (1H, d, J=2.2 Hz), 11.28 (1H, s).

25 (2) Ethyl 4-butoxy-6-chloro-1-oxo-2-propyl-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))

30 Melting point 72-73°C.

Elemental analysis for  $C_{19}H_{24}NO_4Cl$

Calculated: C, 62.38; H, 6.61; N, 3.83.

Found: C, 62.32; H, 6.55; N, 3.56.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.94 (3H, t, J=7.3 Hz), 1.01 (3H, t, J=7.3 Hz), 1.43 (3H, t, J=7.1 Hz), 1.48-1.62 (2H, m), 1.68-1.86 (4H, m), 3.85-3.98 (4H, m), 4.47 (2H, q, J=7.1



Hz), 7.49 (1H, dd, J=2.0, 8.7 Hz), 7.69 (1H, d, J=2.0 Hz), 8.37 (1H, d, J=8.7 Hz).

(3) 4-Butoxy-6-chloro-1-oxo-2-propyl-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 175-176°C.

Elemental analysis for  $C_{17}H_{20}NO_4Cl$ .

Calculated: C, 60.45; H, 5.97; N, 4.15.

Found: C, 60.45; H, 6.27; N, 3.98.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.91-1.06 (6H, m), 1.50-1.65 (2H, m), 1.80-1.85 (4H, m), 3.95-4.04 (4H, m), 7.46 (1H, dd, J=2.0, 8.6 Hz), 7.70 (1H, d, J=2.0 Hz), 8.36 (1H, d, J=8.6 Hz).

(4) 4-Butoxy-6-chloro-3-hydroxymethyl-2-propyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

Melting point 108-109°C.

Elemental analysis for  $C_{17}H_{22}NO_3Cl$ .

Calculated: C, 63.06; H, 6.85; N, 4.33.

Found: C, 62.75; H, 6.89; N, 4.12.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.00 (3H, t, J=7.6 Hz), 1.04 (3H, t, J=7.0 Hz), 1.49-1.92 (6H, m), 2.43 (2H, t, J=6.6 Hz), 4.79 (1H, t, J=5.6 Hz), 3.87 (2H, t, J=6.6 Hz), 4.12-4.20 (2H, m), 4.79 (2H, d, J=5.6 Hz), 7.41 (1H, dd, J=2.0, 8.6 Hz), 7.61 (1H, d, J=2.0 Hz), 8.29 (1H, d, J=8.6 Hz).

(5) 4-Butoxy-6-chloro-3-chloromethyl-2-propyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.02 (3H, t, J=7.4 Hz), 1.05 (3H, t, J=7.2 Hz), 1.56-1.97 (6H, m), 3.99 (2H, t, J=6.5 Hz), 4.11-4.19 (2H, m), 4.78 (2H, s), 7.47 (1H, dd, J=2.2, 8.6 Hz), 7.70 (1H, d, J=2.2 Hz), 8.37 (1H, d, J=8.6 Hz).

(6) 2-((4-Butoxy-6-chloro-1-oxo-2-propyl-1,2-dihydro-3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in

## Example 4 (6))

Melting point 153-154°C.

Elemental analysis for  $C_{25}H_{25}N_2O_4Cl$ 

Calculated: C, 66.29; H, 5.56; N, 6.18.

5 Found: C, 66.31; H, 5.48; N, 6.08.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.80 (3H, t,  $J=7.3$  Hz), 0.92 (3H, t,  $J=7.4$  Hz), 1.38-1.58 (4H, m), 1.69-1.82 (2H, m), 3.89-4.02 (4H, m), 5.02 (2H, s), 7.59 (1H, dd,  $J=2.0, 8.6$  Hz), 7.65 (1H, d,  $J=2.0$  Hz), 7.83-7.92 (4H, m), 8.24 (1H, d,  $J=8.6$  Hz).

(7) Tert-butyl (4-butoxy-6-chloro-1-oxo-2-propyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

15 Melting point 120-121°C.

Elemental analysis for  $C_{22}H_{31}N_2O_4Cl$ 

Calculated: C, 62.48; H, 7.39; N, 6.62.

Found: C, 62.53; H, 7.40; N, 6.49.

20  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.01 (3H, t,  $J=7.4$  Hz), 1.04 (3H, t,  $J=6.8$  Hz), 1.47 (9H, s), 1.52-1.90 (4H, m), 3.84 (2H, t,  $J=6.6$  Hz), 4.01-4.08 (2H, m), 4.50 (2H, d,  $J=5.6$  Hz), 4.77 (1H, bs), 7.43 (1H, dd,  $J=2.0, 8.6$  Hz), 7.64 (1H, d,  $J=2.0$  Hz), 8.34 (1H, d,  $J=8.6$  Hz).

(8) 3-(Aminomethyl)-4-butoxy-6-chloro-2-propyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 124-125°C.

Elemental analysis for  $C_{17}H_{24}N_2O_2Cl_2 \cdot 1/4H_2O$ 

Calculated: C, 56.13; H, 6.79; N, 7.70.

30 Found: C, 56.15; H, 6.82; N, 7.53.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.95 (3H, t,  $J=7.4$  Hz), 1.00 (3H, t,  $J=7.3$  Hz), 1.46-1.68 (4H, m), 1.78-1.92 (2H, m), 3.93 (2H, t,  $J=6.6$  Hz), 3.93-4.02 (2H, m), 4.16 (2H, s), 7.66 (1H, dd,  $J=2.0, 8.4$  Hz), 7.72 (1H, d,  $J=2.0$  Hz), 8.28 (1H, d,  $J=8.4$  Hz), 8.75 (3H, bs).

## Example 26

3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-isobutyl-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 6,7-dichloro-4-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according

5 to the method similar to that in Example 1 (1))

Melting point 111-112°C.

Elemental analysis for  $C_{16}H_{17}NO_4Cl_2$

Calculated: C, 53.65; H, 4.78; N, 3.91.

Found: C, 53.62; H, 4.65; N, 3.66.

10  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.82 (6H, d,  $J=6.6$  Hz), 1.46 (3H, t,  $J=7.2$  Hz), 1.73-1.87 (1H, m), 4.38 (2H, d,  $J=7.8$  Hz), 4.50 (2H, q,  $J=7.2$  Hz), 8.23 (1H, s), 8.53 (1H, s), 11.16 (1H, s).

(2) Ethyl 4-butoxy-6,7-dichloro-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according

15 to the method similar to that in Example 1 (2))

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.90 (6H, d,  $J=6.8$  Hz), 1.01 (3H, t,  $J=7.4$  Hz), 1.44 (3H, t,  $J=7.1$  Hz), 1.48-1.62 (2H, m), 1.72-1.85 (2H, m), 2.05-2.17 (1H, m), 3.88 (2H, d,  $J=7.6$  Hz), 3.94 (2H, t,  $J=6.5$  Hz), 4.46 (2H, q,  $J=7.1$  Hz), 7.81 (1H, s), 8.51 (1H, s).

(3) 4-Butoxy-6,7-dichloro-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

25 Melting point 104-105°C.

Elemental analysis for  $C_{18}H_{21}NO_4Cl_2$

Calculated: C, 55.97; H, 5.48; N, 3.63.

Found: C, 55.82; H, 5.43; N, 3.46.

30  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.91 (6H, d,  $J=6.6$  Hz), 1.00 (3H, t,  $J=7.3$  Hz), 1.45-1.64 (2H, m), 1.75-1.86 (2H, m), 2.08-2.22 (1H, m), 3.97-4.05 (4H, m), 7.65 (1H, s), 8.45 (1H, s).

(4) 4-Butoxy-6,7-dichloro-3-hydroxymethyl-2-isobutyl-1(2H)-isoquinolinone (synthesized according to the

35 method similar to that in Example 4 (4))

Melting point 99-100°C.

Elemental analysis for  $C_{18}H_{23}NO_3Cl_2$

Calculated: C, 58.07; H, 6.23; N, 3.76.

Found: C, 57.90; H, 6.09; N, 3.46.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.92 (6H, d,  $J=6.6$  Hz), 1.05 (3H, t,  $J=7.3$  Hz), 1.50-1.69 (2H, m), 1.80-1.94 (2H, m), 2.04-2.21 (1H, m), 2.57 (1H, bs), 3.88 (2H, t,  $J=6.6$  Hz), 4.09 (2H, d,  $J=7.8$  Hz), 4.79 (2H, d,  $J=4.8$  Hz), 7.69 (1H, d,  $J=2.0$  Hz), 8.35 (1H, d,  $J=2.0$  Hz).

(5) 4-Butoxy-3-chloromethyl-6,7-dichloro-2-isobutyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.95 (6H, d,  $J=7.0$  Hz), 1.05 (3H, t,  $J=7.3$  Hz), 1.51-1.66 (2H, m), 1.82-1.96 (2H, m), 2.04-2.21 (1H, m), 3.97 (2H, t,  $J=6.5$  Hz), 4.06 (2H, d,  $J=5.8$  Hz), 4.77 (2H, s), 7.81 (1H, s), 8.50 (1H, s).

(6) 2-((4-Butoxy-6,7-dichloro-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 103-104°C.

Elemental analysis for  $C_{26}H_{26}N_2O_4Cl_2$

Calculated: C, 62.28; H, 5.23; N, 5.59.

Found: C, 62.18; H, 5.03; N, 5.53.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.95 (6H, d,  $J=6.6$  Hz), 1.00 (3H, t,  $J=7.4$  Hz), 1.43-1.58 (2H, m), 1.79-1.92 (2H, m), 2.07-2.21 (1H, m), 3.94-4.04 (4H, m), 5.01 (2H, s), 7.70-7.90 (5H, m), 8.49 (1H, s).

(7) Tert-butyl (4-butoxy-6,7-dichloro-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

Melting point 138-139°C.

Elemental analysis for  $C_{23}H_{32}N_2O_4Cl_2$

Calculated: C, 58.85; H, 6.44; N, 5.97.

Found: C, 58.60; H, 6.64; N, 5.72.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.95 (6H, d,  $J=6.6$  Hz), 1.04 (3H, t,

J=7.3 Hz), 1.47 (9H, s), 1.47-1.67 (2H, m), 1.79-1.93 (2H, m), 2.07-2.21 (1H, m), 3.84 (2H, t, J=6.5 Hz), 3.98 (2H, d, J=7.4 Hz), 4.49 (2H, d, J=5.4 Hz), 4.80 (1H, bs), 7.75 (1H, s), 8.45 (1H, s).

- 5 (8) 3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-isobutyl-1(2H)-isoquinoline hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 168-170°C.

Elemental analysis for  $C_{18}H_{25}N_2O_2Cl_3$

- 10 Calculated: C, 53.02; H, 6.18; N, 6.87.

Found: C, 53.28; H, 6.13; N, 6.76.

- $^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.88 (6H, d, J=6.6 Hz), 1.00 (3H, t, J=7.1 Hz), 1.45-1.63 (2H, m), 1.78-1.96 (2H, m), 1.99-2.09 (1H, m), 3.91-3.99 (4H, m), 4.17 (2H, s), 7.92 (1H, s), 8.38 (1H, s), 8.68 (3H, bs).

#### Example 27

3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-neopentyl-1(2H)-isoquinolinone hydrochloride

- 20 (1) Ethyl 6,7-dichloro-4-hydroxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (1))

Melting point 117-118°C.

Elemental analysis for  $C_{17}H_{19}NO_4Cl_2$

Calculated: C, 54.85; H, 5.14; N, 3.76.

- 25 Found: C, 54.89; H, 5.14; N, 3.62.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.84 (9H, s), 1.47 (3H, t, J=7.1 Hz), 4.49 (2H, q, J=7.1 Hz), 4.51 (2H, bs), 8.22 (1H, s), 8.52 (1H, s), 10.73 (1H, s).

- 30 (2) Ethyl 4-butoxy-6,7-dichloro-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))

- $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.93 (9H, s), 1.02 (3H, t, J=7.3 Hz), 1.44 (3H, t, J=7.1 Hz), 1.48-1.59 (2H, m), 1.73-1.83 (2H, m), 3.94 (2H, t, J=6.6 Hz), 4.07 (2H, bs), 4.43 (2H, q, J=7.1 Hz), 7.83 (1H, s), 8.51 (1H, s).

(3) 4-Butoxy-6,7-dichloro-2-neopentyl-1-oxo-1,2-dihydro-

3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 138-139°C.

Elemental analysis for  $C_{19}H_{23}NO_4Cl_2$

5 Calculated: C, 57.01; H, 5.79; N, 3.50.

Found: C, 57.03; H, 5.86; N, 3.30.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.93 (9H, s), 1.01 (3H, t,  $J=7.1$  Hz),  
1.40-1.64 (2H, m), 1.77-1.91 (2H, m), 4.00 (2H, t,  $J=6.6$   
Hz), 4.23 (2H, bs), 5.81 (1H, bs), 7.77 (1H, s), 8.45  
10 (1H, s).

(4) 4-Butoxy-6,7-dichloro-3-hydroxymethyl-2-neopentyl-  
1(2H)-isoquinolinone (synthesized according to the  
method similar to that in Example 4 (4))

Melting point 178-179°C.

15 Elemental analysis for  $C_{19}H_{25}NO_3Cl_2$

Calculated: C, 59.07; H, 6.52; N, 3.63.

Found: C, 59.00; H, 6.39; N, 3.33.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.93 (9H, s), 1.06 (3H, t,  $J=7.3$  Hz),  
1.56-1.67 (2H, m), 1.81-1.92 (2H, m), 3.08 (1H, t,  $J=5.9$   
20 Hz), 3.90 (2H, t,  $J=6.4$  Hz), 4.20 (2H, bs), 4.84 (2H,  
bs), 7.66 (1H, s), 8.22 (1H, s).

(5) 4-Butoxy-3-chloromethyl-6,7-dichloro-2-neopentyl-  
1(2H)-isoquinolinone (synthesized according to the  
method similar to that in Example 4 (5))

25  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.98 (9H, s), 1.05 (3H, t,  $J=7.3$  Hz),  
1.55-1.70 (2H, m), 1.82-1.95 (2H, m), 3.93 (2H, t,  $J=6.6$   
Hz), 4.17 (2H, bs), 4.84 (2H, bs), 7.80 (1H, s), 8.50  
(1H, s).

(6) 2-((4-Butoxy-6,7-dichloro-2-neopentyl-1-oxo-1,2-  
30 dihydro-3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-  
dione (synthesized according to the method similar to  
that in Example 4 (6))

Melting point 145-146°C.

Elemental analysis for  $C_{27}H_{28}N_2O_4Cl_2$

35 Calculated: C, 62.92; H, 5.48; N, 5.43.

Found: C, 62.76; H, 5.76; N, 5.22.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 1.00 (9H, s), 1.01 (3H, t,  $J=7.1$  Hz), 1.49-1.61 (2H, m), 1.81-1.95 (2H, m), 4.00 (2H, t,  $J=6.8$  Hz), 4.07 (2H, bs), 5.05 (2H, s), 7.70-7.86 (5H, m), 8.47 (1H, s).

- 5 (7) Tert-butyl (4-butoxy-6,7-dichloro-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

Melting point 152-153°C.

- 10 Elemental analysis for  $\text{C}_{24}\text{H}_{34}\text{N}_2\text{O}_4\text{Cl}_2$

Calculated: C, 59.39; H, 7.06; N, 5.77.

Found: C, 59.15; H, 7.10; N, 5.54.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.98 (9H, s), 1.01 (3H, t,  $J=7.0$  Hz), 1.46 (9H, s), 1.53-1.68 (2H, m), 1.80-1.94 (2H, m), 3.85 (2H, t,  $J=6.6$  Hz), 4.11-4.28 (2H, m), 4.55 (2H, d,  $J=5.4$  Hz), 4.83 (1H, bs), 7.74 (1H, d,  $J=1.7$  Hz), 8.41 (1H, d,  $J=1.7$  Hz).

- 15 (8) 3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-neopentyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 157-158°C.

Elemental analysis for  $\text{C}_{19}\text{H}_{27}\text{N}_2\text{O}_2\text{Cl}_3 \cdot 1/2\text{H}_2\text{O}$

Calculated: C, 52.97; H, 6.55; N, 6.50.

- 25 Found: C, 53.04; H, 6.59; N, 6.46.

$^1\text{H-NMR}(\text{DMSO}-d_6)$   $\delta$ : 0.91 (9H, s), 0.99 (3H, t,  $J=7.1$  Hz), 1.45-1.60 (2H, m), 1.77-1.91 (2H, m), 3.95 (2H, t,  $J=6.4$  Hz), 4.11 (2H, bs), 4.24 (2H, bs), 7.92 (1H, s), 8.38 (1H, s), 8.62 (3H, bs).

- 30 Example 28

3-(Aminomethyl)-2-benzyl-4-butoxy-6,7-dichloro-1(2H)-isoquinolinone hydrochloride

- (1) Ethyl 2-benzyl-6,7-dichloro-4-hydroxy-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (1))

Melting point 140-141°C.

Elemental analysis for  $C_{19}H_{15}NO_4Cl_2$

Calculated: C, 58.18; H, 3.85; N, 3.57.

Found: C, 58.22; H, 3.98; N, 3.27.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.18 (3H, t,  $J=7.2$  Hz), 4.28 (2H, q,  $J=7.2$  Hz), 5.60 (2H, s), 7.03-7.07 (2H, m), 7.20-7.32 (3H, m), 8.26 (1H, s), 8.57 (1H, s), 11.20 (1H, s).

(2) Ethyl 2-benzyl-4-butoxy-6,7-dichloro-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.98 (3H, t,  $J=7.3$  Hz), 1.13 (3H, t,  $J=7.2$  Hz), 1.40-1.59 (2H, m), 1.70-1.83 (2H, m), 3.92 (2H, t,  $J=6.4$  Hz), 4.17 (2H, q,  $J=7.2$  Hz), 5.34 (2H, s), 7.16-7.31 (5H, m), 7.83 (1H, s), 8.56 (1H, s).

(3) 2-Benzyl-4-butoxy-6,7-dichloro-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 128-129°C.

Elemental analysis for  $C_{21}H_{19}NO_4Cl_2$

Calculated: C, 60.01; H, 4.59; N, 3.33.

Found: C, 60.00; H, 4.40; N, 3.11.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.97 (3H, t,  $J=7.3$  Hz), 1.41-1.60 (2H, m), 1.72-1.86 (2H, m), 3.97 (2H, t,  $J=6.4$  Hz), 4.83 (1H, bs), 5.42 (2H, s), 7.18-7.26 (5H, m), 7.83 (1H, s), 8.53 (1H, s).

(4) 2-Benzyl-4-butoxy-6,7-dichloro-3-hydroxymethyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

Melting point 110-111°C.

Elemental analysis for  $C_{21}H_{21}NO_3Cl_2$

Calculated: C, 62.08; H, 5.21; N, 3.45.

Found: C, 62.01; H, 5.28; N, 3.25.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.02 (3H, t,  $J=7.1$  Hz), 1.47-1.65 (2H, m), 1.77-1.91 (2H, m), 2.23 (1H, bs), 3.87 (2H, t,  $J=6.6$  Hz), 4.65 (2H, d,  $J=5.6$  Hz), 5.59 (2H, s), 7.12-7.16 (2H, m), 7.25-7.34 (3H, m), 7.78 (1H, d,  $J=1.7$  Hz), 8.50 (1H, d,  $J=1.7$  Hz).



(5) 2-Benzyl-4-butoxy-3-chloromethyl-6,7-dichloro-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:1.03 (3H, d, J=7.2 Hz), 1.53-1.64 (2H, m), 1.80-1.95 (2H, m), 4.00 (2H, t, J=6.4 Hz), 4.60 (2H, s), 5.60 (2H, s), 7.10-7.34 (5H, m), 7.85 (1H, s), 8.58 (1H, s).

(6) 2-((2-Benzyl-4-butoxy-6,7-dichloro-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 161-162°C.

Elemental analysis for C<sub>29</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>Cl<sub>2</sub>

Calculated: C, 65.05; H, 4.52; N, 5.23.

Found: C, 64.98; H, 4.64; N, 5.07.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:1.01 (3H, t, J=7.3 Hz), 1.47-1.65 (2H, m), 1.80-1.94 (2H, m), 4.12 (2H, t, J=6.7 Hz), 5.02 (2H, s), 5.37 (2H, s), 6.65-6.72 (1H, m), 6.78-6.92 (4H, m), 7.51-7.60 (4H, m), 7.90 (1H, s), 8.53 (1H, s).

(7) Tert-butyl (2-benzyl-4-butoxy-6,7-dichloro-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

Melting point 151-152°C.

Elemental analysis for C<sub>26</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>Cl<sub>2</sub>

Calculated: C, 61.78; H, 5.98; N, 5.54.

Found: C, 61.73; H, 6.17; N, 5.45.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:1.02 (3H, t, J=7.3 Hz), 1.42 (9H, s), 1.47-1.60 (2H, m), 1.76-1.87 (2H, m), 3.83 (2H, t, J=6.6 Hz), 4.38 (2H, d, J=6.0 Hz), 4.74 (1H, bs), 5.45 (2H, s), 7.19-7.35 (5H, m), 7.78 (1H, s), 8.53 (1H, s).

(8) 3-(Aminomethyl)-2-benzyl-4-butoxy-6,7-dichloro-1(2H)-isoquinoline hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 191-192°C.

Elemental analysis for C<sub>21</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub>Cl<sub>3</sub>

Calculated: C, 57.09; H, 5.25; N, 6.34.

Found: C, 56.77; H, 5.14; N, 6.04.

$^1\text{H-NMR}$ (DMSO- $d_6$ )  $\delta$ : 0.97 (3H, t,  $J=7.3$  Hz), 1.43-1.59 (2H, m), 1.76-1.90 (2H, m), 3.91-3.98 (4H, m), 5.47 (2H, s), 7.18-7.22 (2H, m), 7.28-7.39 (3H, m), 7.96 (1H, s), 8.43 (1H, s), 8.89 (3H, bs).

#### Example 29

3-(Aminomethyl)-6,7-dichloro-2-isobutyl-4-pentyloxy-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 6,7-dichloro-2-isobutyl-1-oxo-4-pentyloxy-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))

$^1\text{H-NMR}$ ( $\text{CDCl}_3$ )  $\delta$ : 0.90 (6H, d,  $J=6.6$  Hz), 0.96 (3H, t,  $J=6.6$  Hz), 1.29-1.54 (7H, m), 1.74-1.87 (2H, m), 2.05-2.17 (1H, m), 3.90 (2H, d,  $J=5.8$  Hz), 3.93 (2H, t,  $J=6.6$  Hz), 4.46 (2H, q,  $J=7.1$  Hz), 7.81 (1H, s), 8.51 (1H, s).

(2) 6,7-Dichloro-2-isobutyl-1-oxo-4-pentyloxy-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4

(3))

Melting point 124-125°C.

Elemental analysis for  $\text{C}_{19}\text{H}_{23}\text{NO}_4\text{Cl}_2$

Calculated: C, 57.01; H, 5.79; N, 3.50.

Found: C, 57.13; H, 5.72; N, 3.40.

$^1\text{H-NMR}$ ( $\text{CDCl}_3$ )  $\delta$ : 0.90 (6H, d,  $J=6.6$  Hz), 0.95 (3H, t,  $J=6.6$  Hz), 1.31-1.57 (4H, m), 1.77-1.91 (2H, m), 2.07-2.21 (1H, m), 3.95-4.04 (4H, m), 4.35 (1H, bs), 7.75 (1H, s), 8.45 (1H, s).

(3) 6,7-Dichloro-3-hydroxymethyl-2-isobutyl-4-pentyloxy-

1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

Melting point 86-87°C.

Elemental analysis for  $\text{C}_{19}\text{H}_{25}\text{NO}_3\text{Cl}_2$

Calculated: C, 59.07; H, 6.52; N, 3.63.

Found: C, 58.91; H, 6.65; N, 3.48.

$^1\text{H-NMR}$ ( $\text{CDCl}_3$ )  $\delta$ : 0.82 (6H, d,  $J=6.6$  Hz), 0.99 (3H, t,

J=7.0 Hz), 1.39-1.59 (4H, m), 1.82-1.92 (2H, m), 2.07-2.17 (1H, m), 2.67 (1H, bs), 3.87 (2H, t, J=6.4 Hz), 4.09 (2H, d, J=7.6 Hz), 4.78 (2H, d, J=4.8 Hz), 7.69 (1H, s), 8.35 (1H, s).

- 5 (4) 3-Chloromethyl-6,7-dichloro-2-isobutyl-4-pentyloxy-1(2H)-isoquinoline (synthesized according to the method similar to that in Example 4 (5)).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.96 (6H, d, J=6.6 Hz), 0.99 (3H, t, J=7.0 Hz), 1.36-1.61 (4H, m), 1.84-1.98 (2H, m), 2.05-2.22 (1H, m), 3.96 (2H, t, J=6.4 Hz), 4.07 (2H, d, J=7.6 Hz), 4.78 (2H, s), 7.81 (1H, s), 8.51 (1H, s).

- 10 (5) 2-((6,7-Dichloro-2-isobutyl-1-oxo-4-pentyloxy-1,2-dihydro-3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 119-120°C.

Elemental analysis for C<sub>27</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>Cl<sub>2</sub>

Calculated: C, 62.92; H, 5.48; N, 5.43.

Found: C, 62.95; H, 5.43; N, 5.55.

- 20 <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.88-1.04 (9H, m), 1.30-1.54 (4H, m), 1.80-1.90 (2H, m), 2.05-2.17 (1H, m), 3.90-4.05 (4H, m), 5.06 (2H, s), 7.70-7.89 (5H, m), 8.49 (1H, s).

- (6) Tert-butyl (6,7-dichloro-2-isobutyl-1-oxo-4-pentyloxy-1,2-dihydro-3-isoquinolinyl)methylcarbamate  
25 (synthesized according to the method similar to that in Example 1 (6)).

Melting point 113-114°C.

Elemental analysis for C<sub>24</sub>H<sub>34</sub>N<sub>2</sub>O<sub>4</sub>Cl<sub>2</sub>

Calculated: C, 59.39; H, 7.06; N, 5.77.

- 30 Found: C, 59.39; H, 7.00; N, 5.67.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.95 (6H, d, J=6.6 Hz), 0.98 (3H, t, J=7.1 Hz), 1.38-1.57 (13H, m), 1.81-1.95 (2H, m), 2.07-2.21 (1H, m), 3.84 (2H, t, J=6.6 Hz), 3.97 (2H, d, J=7.4 Hz), 4.49 (2H, d, J=5.4 Hz), 4.81 (1H, bs), 7.75 (1H, s),  
35 8.46 (1H, s).

- (7) 3-(Aminomethyl)-6,7-dichloro-2-isobutyl-4-pentyloxy-

1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 167-169°C.

5 Elemental analysis for  $C_{19}H_{27}N_2O_2Cl_3$

Calculated: C, 54.10; H, 6.45; N, 6.64.

Found: C, 54.09; H, 6.45; N, 6.54.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.88 (6H, d,  $J=7.0$  Hz), 0.95 (3H, t,  $J=7.0$  Hz), 1.31-1.57 (4H, m), 1.80-2.10 (3H, m), 3.91-3.99 (4H, m), 4.17 (2H, s), 7.92 (1H, s), 8.38 (1H, s), 8.72 (3H, bs).

### Example 30

3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-isopropyl-1(2H)-isoquinolinone hydrochloride

15 (1) Ethyl 6,7-dichloro-4-hydroxy-2-isopropyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (1))

Melting point 124-125°C.

Elemental analysis for  $C_{15}H_{15}NO_4Cl_2 \cdot 1/2H_2O$

20 Calculated: C, 51.01; H, 4.57; N, 3.97.

Found: C, 51.23; H, 4.25; N, 3.86.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.45 (3H, t,  $J=7.1$  Hz), 1.62 (6H, d,  $J=6.6$  Hz), 4.19-4.33 (1H, m), 4.47 (2H, q,  $J=7.1$  Hz), 8.17 (1H, s), 8.46 (1H, s), 10.64 (1H, s).

25 (2) Ethyl 4-butoxy-6,7-dichloro-2-isopropyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.01 (3H, t,  $J=7.1$  Hz), 1.44 (3H, t,  $J=7.2$  Hz), 1.46-1.59 (2H, m), 1.64 (6H, d,  $J=6.6$  Hz), 1.71-1.85 (2H, m), 3.93 (2H, t,  $J=6.4$  Hz), 4.01-4.18 (1H, m), 4.45 (2H, q,  $J=7.2$  Hz), 7.77 (1H, s), 8.47 (1H, s).

(3) 4-Butoxy-6,7-dichloro-2-isopropyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

35 Melting point 186-187°C.

Elemental analysis for  $C_{17}H_{19}NO_4Cl_2$

Calculated: C, 54.85; H, 5.14; N, 3.76.

Found: C, 54.90; H, 5.12; N, 3.68.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.99 (3H, t,  $J=7.3$  Hz), 1.44-1.62 (2H, m), 1.68 (6H, d,  $J=6.6$  Hz), 1.74-1.88 (2H, m), 4.00 (2H, t,  $J=6.4$  Hz), 4.21-4.34 (1H, m), 5.11 (1H, bs), 7.80 (1H, s), 8.51 (1H, s).

(4) 4-Butoxy-6,7-dichloro-3-hydroxymethyl-2-isopropyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

10 Melting point 150-151°C.

Elemental analysis for  $\text{C}_{17}\text{H}_{21}\text{NO}_3\text{Cl}_2 \cdot 1/4\text{H}_2\text{O}$

Calculated: C, 56.29; H, 5.97; N, 3.86.

Found: C, 56.53; H, 6.01; N, 3.96.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 1.03 (3H, t,  $J=7.4$  Hz), 1.44-1.66 (2H, m), 1.67 (6H, d,  $J=7.0$  Hz), 1.78-1.92 (2H, m), 2.04 (1H, bs), 3.85 (2H, t,  $J=6.6$  Hz), 4.64-4.74 (1H, m), 4.81 (2H, s), 7.73 (1H, s), 8.44 (1H, s).

(5) 4-Butoxy-3-chloromethyl-6,7-dichloro-2-isopropyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 1.05 (3H, t,  $J=7.1$  Hz), 1.51-1.66 (2H, m), 1.70 (6H, d,  $J=6.6$  Hz), 1.78-1.95 (2H, m), 3.96 (2H, t,  $J=6.4$  Hz), 4.47-4.60 (1H, m), 4.77 (2H, s), 7.77 (1H, s), 8.46 (1H, s).

25 (6) 2-[(4-Butoxy-6,7-dichloro-2-isopropyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 185-186°C.

30 Elemental analysis for  $\text{C}_{25}\text{H}_{24}\text{N}_2\text{O}_4\text{Cl}_2$

Calculated: C, 61.61; H, 4.96; N, 5.75.

Found: C, 61.71; H, 4.89; N, 5.66.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 1.01 (3H, t,  $J=7.4$  Hz), 1.47 (6H, d,  $J=6.6$  Hz), 1.48-1.68 (2H, m), 1.80-1.94 (2H, m), 4.05 (2H, t,  $J=6.6$  Hz), 4.19-4.32 (1H, m), 5.09 (2H, s), 7.73-7.89 (5H, m), 8.43 (1H, s).

(7) Tert-butyl (4-butoxy-6,7-dichloro-2-isopropyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6).)

5 Melting point 169.5-170°C.

Elemental analysis for  $C_{22}H_{30}N_2O_4Cl_2$

Calculated: C, 57.77; H, 6.61; N, 6.12.

Found: C, 57.74; H, 6.76; N, 6.13.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.03 (3H, t,  $J=7.4$  Hz), 1.47 (9H, s),  
10 1.48-1.62 (2H, m), 1.63 (6H, d,  $J=6.6$  Hz), 1.71-1.92 (2H, m), 3.81 (2H, t,  $J=6.4$  Hz), 4.41-4.52 (1H, m), 4.53 (2H, d,  $J=5.4$  Hz), 4.67 (1H, bs), 7.73 (1H, s), 8.45 (1H, s).

(8) 3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-isopropyl-1(2H)-isoquinolinone hydrochloride (synthesized  
15 according to the method similar to that in Example 1 (7))

Melting point 264-265°C.

Elemental analysis for  $C_{17}H_{23}N_2O_2Cl_3$

Calculated: C, 51.86; H, 5.89; N, 7.11.

20 Found: C, 52.00; H, 5.70; N, 7.18.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.99 (3H, t,  $J=7.1$  Hz), 1.45-1.56 (2H, m), 1.57 (6H, d,  $J=6.6$  Hz), 1.77-1.91 (2H, m), 3.90 (2H, t,  $J=6.4$  Hz), 4.23 (2H, s), 4.36-4.49 (1H, m), 7.87 (1H, s), 8.34 (1H, s), 8.85 (3H, bs).

25 **Example 31**

3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-cyclopropyl-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 2-cyclopropyl-6,7-dichloro-4-hydroxy-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized  
30 according to the method similar to that in Example 1 (1))

Melting point 119.5-120°C.

Elemental analysis for  $C_{15}H_{13}NO_4Cl_2$

Calculated: C, 52.63; H, 3.83; N, 4.09.

35 Found: C, 52.97; H, 3.90; N, 3.78.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.62-0.70 (2H, m), 1.05-1.16 (2H, m),

1.44 (3H, t, J=7.2 Hz), 3.33-3.44 (1H, m), 4.48 (2H, q, J=7.2 Hz), 8.16 (1H, s), 8.47 (1H, s), 10.58 (1H, s).

- (2) Ethyl 4-butoxy-6,7-dichloro-2-cyclopropyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))

Melting point 72.5-73.5°C.

Elemental analysis for  $C_{19}H_{21}NO_4Cl_2$

Calculated: C, 57.30; H, 5.31; N, 3.52.

Found: C, 57.24; H, 5.24; N, 3.47.

- <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.82-0.91 (2H, m), 1.01 (3H, t, J=7.3 Hz), 1.01-1.15 (2H, m), 1.44 (3H, t, J=7.2 Hz), 1.43-1.60 (2H, m), 1.72-1.86 (2H, m), 3.10-3.22 (1H, m), 3.94 (2H, t, J=6.5 Hz), 4.46 (2H, q, J=7.2 Hz), 7.80 (1H, s), 8.47 (1H, s).

- (3) 4-Butoxy-6,7-dichloro-2-cyclopropyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 198-201°C.

- Elemental analysis for  $C_{17}H_{17}NO_4Cl_2$

Calculated: C, 55.15; H, 4.68; N, 3.78.

Found: C, 55.14; H, 4.47; N, 3.73.

- <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.85-0.94 (2H, m), 1.00 (3H, t, J=7.3 Hz), 1.14-1.30 (2H, m), 1.42-1.63 (2H, m), 1.75-1.89 (2H, m), 3.26-3.35 (1H, m), 4.00 (2H, t, J=6.4 Hz), 5.55 (1H, bs), 7.75 (1H, s), 8.41 (1H, s).

(4) 4-Butoxy-6,7-dichloro-2-cyclopropyl-3-hydroxymethyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

- Melting point 145-146°C.

Elemental analysis for  $C_{17}H_{19}NO_3Cl_2$

Calculated: C, 57.32; H, 5.38; N, 3.93.

Found: C, 57.28; H, 5.17; N, 3.97.

- <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.82-0.91 (2H, m), 1.06 (3H, t, J=7.2 Hz), 1.21-1.32 (2H, m), 1.51-1.70 (2H, m), 1.80-1.94 (2H, m), 3.04 (1H, bs), 3.13-3.22 (1H, m), 3.90 (2H, t, J=6.4

Hz), 4.98 (2H, d, J=5.8 Hz), 7.65 (1H, s), 8.25 (1H, s).

(5) 4-Butoxy-3-chloromethyl-6,7-dichloro-2-cyclopropyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.87-0.95 (2H, m), 1.04 (3H, t, J=7.4 Hz), 1.22-1.37 (2H, m), 1.50-1.69 (2H, m), 1.80-1.95 (2H, m), 3.14-3.25 (1H, m), 3.93 (2H, t, J=6.6 Hz), 5.03 (2H, s), 7.76 (1H, s), 8.45 (1H, s).

(6) 2-(4-Butoxy-6,7-dichloro-2-cyclopropyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 197-198°C.

Elemental analysis for C<sub>25</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>Cl<sub>2</sub>

Calculated: C, 61.87; H, 4.57; N, 5.77.

Found: C, 61.93; H, 4.50; N, 5.84.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.82-0.91 (2H, m), 1.00 (3H, t, J=7.3 Hz), 1.26-1.37 (2H, m), 1.43-1.61 (2H, m), 1.75-1.90 (2H, m), 2.84-2.95 (1H, m), 3.98 (2H, t, J=6.8 Hz), 5.25 (2H, s), 7.69-7.84 (5H, m), 8.42 (1H, s).

(7) Tert-butyl (4-butoxy-6,7-dichloro-2-cyclopropyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

Melting point 143-144°C.

Elemental analysis for C<sub>22</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>Cl<sub>2</sub>

Calculated: C, 58.03; H, 6.20; N, 6.15.

Found: C, 58.09; H, 6.33; N, 5.95.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.79-0.88 (2H, m), 1.04 (3H, t, J=7.3 Hz), 1.25-1.39 (2H, m), 1.44 (9H, s), 1.48-1.67 (2H, m), 1.76-1.93 (2H, m), 2.97-3.08 (1H, m), 3.86 (2H, t, J=6.6 Hz), 4.73 (2H, d, J=5.6 Hz), 4.95 (1H, bs), 7.71 (1H, s), 8.38 (1H, s).

(8) 3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-cyclopropyl-1(2H)-isoquinoline hydrochloride (synthesized according to the method similar to that in Example 1 (7))



Melting point 238°C.

Elemental analysis for  $C_{17}H_{21}N_2O_2Cl_3$

Calculated: C, 52.12; H, 5.40; N, 7.15.

Found: C, 51.96; H, 5.30; N, 6.99.

- 5  $^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.84-0.92 (2H, m), 0.99 (3H, t,  $J=7.3$  Hz), 1.19-1.30 (2H, m), 1.44-1.63 (2H, m), 1.77-1.91 (2H, m), 3.13-3.21 (1H, m), 3.93 (2H, t,  $J=6.0$  Hz), 4.38 (2H, bs), 7.85 (1H, s), 8.30 (1H, s), 8.78 (3H, bs).

Example 32

- 10 3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-cyclopropylmethyl-1(2H)-isoquinoline hydrochloride  
(1) Ethyl 6,7-dichloro-2-cyclopropylmethyl-4-hydroxy-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1

- 15 (1))

Melting point 109.5-110°C.

Elemental analysis for  $C_{16}H_{15}NO_4Cl_2$

Calculated: C, 53.95; H, 4.24; N, 3.93.

Found: C, 54.03; H, 4.04; N, 3.95.

- 20  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.32-0.54 (4H, m), 0.96-1.16 (1H, m), 1.48 (3H, t,  $J=7.2$  Hz), 4.33 (2H, d,  $J=6.8$  Hz), 4.52 (2H, q,  $J=7.2$  Hz), 8.23 (1H, s), 8.51 (1H, s), 11.17 (1H, s).

- (2) Ethyl 4-butoxy-6,7-dichloro-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1

- 25 (2))

- $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.38-0.57 (4H, m), 1.01 (3H, t,  $J=7.4$  Hz), 1.16-1.26 (1H, m), 1.45 (3H, t,  $J=7.4$  Hz), 1.47-1.62 (2H, m), 1.68-1.86 (2H, m), 3.89-3.99 (4H, m), 4.47 (2H, q,  $J=7.4$  Hz), 7.81 (1H, s), 8.51 (1H, s).

- 30 (3) 4-Butoxy-6,7-dichloro-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4

(3))

- 35 Melting point 150-151°C.

Elemental analysis for  $C_{18}H_{19}NO_4Cl_2$

Calculated: C, 56.26; H, 4.98; N, 3.65.

Found: C, 56.45; H, 5.02; N, 3.67.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.41-0.58 (4H, m), 1.00 (3H, t, J=7.3 Hz), 1.20-1.33 (1H, m), 1.45-1.64 (2H, m), 1.76-1.90 (2H, m), 4.01 (2H, t, J=6.5 Hz), 4.06 (2H, d, J=7.4 Hz), 7.74 (1H, s), 8.46 (1H, s).

(4) 4-Butoxy-6,7-dichloro-2-cyclopropylmethyl-3-hydroxymethyl-1(2H)-isoquinoline (synthesized according to the method similar to that in Example 4 (4))

10 Melting point 130-130.5°C.

Elemental analysis for C<sub>18</sub>H<sub>21</sub>NO<sub>3</sub>Cl<sub>2</sub>

Calculated: C, 58.39; H, 5.72; N, 3.78.

Found: C, 58.46; H, 5.84; N, 3.77.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.46-0.58 (4H, m), 1.04 (3H, t, J=7.4 Hz), 1.08-1.24 (1H, m), 1.50-1.68 (2H, m), 1.79-1.94 (2H, m), 2.33 (1H, bs), 3.88 (2H, t, J=6.8 Hz), 4.19 (2H, d, J=7.0 Hz), 4.83 (2H, d, J=5.6 Hz), 7.72 (1H, s), 8.42 (1H, s).

(5) 4-Butoxy-3-chloromethyl-6,7-dichloro-2-cyclopropylmethyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.44-0.62 (4H, m), 1.02-1.15 (4H, m), 1.52-1.71 (2H, m), 1.83-1.97 (2H, m), 3.99 (2H, t, J=6.6 Hz), 4.20 (2H, d, J=6.6 Hz), 4.83 (2H, s), 7.81 (1H, s), 8.51 (1H, s).

(6) 2-(4-Butoxy-6,7-dichloro-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinoliny)methyl-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

30 Melting point 162-163°C.

Elemental analysis for C<sub>26</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>Cl<sub>2</sub>

Calculated: C, 62.53; H, 4.84; N, 5.61.

Found: C, 62.64; H, 4.77; N, 5.61.

35 <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.47-0.50 (4H, m), 0.95-1.08 (4H, m), 1.43-1.62 (2H, m), 1.78-1.92 (2H, m), 3.98 (2H, t, J=6.7

Hz), 4.15 (2H, d, J=6.6 Hz), 5.05 (2H, s), 7.71-7.86 (5H, m), 8.49 (1H, s).

(7) Tert-butyl (4-butoxy-6,7-dichloro-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-

5 isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6)).

Melting point 141.5-142.5°C.

Elemental analysis for  $C_{23}H_{30}N_2O_4Cl_2$

Calculated: C, 58.85; H, 6.44; N, 5.97.

10 Found: C, 58.84; H, 6.32; N, 6.04.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.50-0.59 (4H, m), 1.04 (3H, t, J=7.4 Hz), 1.08-1.28 (1H, m), 1.47 (9H, s), 1.53-1.68 (2H, m), 1.80-1.94 (2H, m), 3.86 (2H, t, J=6.4 Hz), 4.08 (2H, d, J=6.6 Hz), 4.52 (2H, d, J=5.8 Hz), 4.87 (1H, bs), 7.74

15 (1H, s), 8.45 (1H, s).

(8) 3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-

cyclopropylmethyl-1(2H)-isoquinoline hydrochloride (synthesized according to the method similar to that in Example 1 (7))

20 Melting point 227-228°C.

Elemental analysis for  $C_{18}H_{23}N_2O_2Cl_2$

Calculated: C, 53.28; H, 5.71; N, 6.90.

Found: C, 53.18; H, 5.71; N, 6.75.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.47 (4H, d, J=6.6 Hz), 1.00 (3H, t, J=7.3 Hz), 1.13-1.26 (1H, m), 1.45-1.64 (2H, m), 1.78-1.92 (4H, m), 3.96 (3H, t, J=6.4 Hz), 4.06 (6H, d, J=6.6 Hz), 4.20 (2H, d, J=4.0 Hz), 7.92 (1H, s), 8.39 (1H, s), 8.72 (3H, bs).

#### Example 33

30 3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-isopentyl-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 6,7-dichloro-4-hydroxy-2-isopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (1))

35 Melting point 118-120°C.

Elemental analysis for  $C_{16}H_{15}NO_4Cl_2$

Calculated: C, 54.85; H, 5.14; N, 3.76.

Found: C, 54.63; H, 5.03; N, 3.52.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.96 (6H, d,  $J=6.2$  Hz), 1.47 (3H, t,  $J=7.2$  Hz), 1.58-1.65 (3H, m), 4.26-4.34 (2H, m), 4.52

(2H, q,  $J=7.2$  Hz), 8.22 (1H, s), 8.51 (1H, s), 11.24 (1H, s).

(2) Ethyl 4-butoxy-6,7-dichloro-2-isopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.95 (6H, d,  $J=6.2$  Hz), 1.01 (3H, t,  $J=7.0$  Hz), 1.39-1.86 (10H, m), 3.91-3.98 (4H, m), 4.46 (2H, q,  $J=7.2$  Hz), 7.80 (1H, s), 8.50 (1H, s).

(3) 4-Butoxy-6,7-dichloro-2-isopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 100-101°C.

Elemental analysis for  $\text{C}_{19}\text{H}_{23}\text{NO}_4\text{Cl}_2$

Calculated: C, 57.01; H, 5.79; N, 3.50.

Found: C, 56.83; H, 5.88; N, 3.51.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.94-1.03 (98H, m), .45-1.88 (7H, m), 3.99 (2H, t,  $J=6.4$  Hz), 4.04-4.11 (2H, m), 5.59 (1H, bs), 7.76 (1H, s), 8.46 (1H, s).

(4) 4-Butoxy-6,7-dichloro-3-hydroxymethyl-2-isopentyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

Melting point 102-103.5°C.

Elemental analysis for  $\text{C}_{19}\text{H}_{25}\text{NO}_3\text{Cl}_2$

Calculated: C, 59.07; H, 6.52; N, 3.63.

Found: C, 58.78; H, 6.64; N, 3.60.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.99 (6H, d,  $J=6.6$  Hz), 1.04 (3H, t,  $J=7.4$  Hz), 1.49-1.92 (7H, m), 2.56 (1H, bs), 3.86 (2H, t,  $J=6.5$  Hz), 4.18-4.26 (2H, m), 4.76 (2H, s), 7.69 (1H, s), 8.38 (1H, s).

(5) 4-Butoxy-3-chloromethyl-6,7-dichloro-2-isopentyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 1.01 (6H, d,  $J=6.2$  Hz), 1.05 (3H, t,  $J=7.3$  Hz), 1.52-1.96 (7H, m), 3.98 (2H, t,  $J=6.4$  Hz), 4.10-4.25 (2H, m), 4.75 (2H, s), 7.81 (1H, s), 8.50 (1H, s).

- 5 (6) 2-[(4-Butoxy-6,7-dichloro-2-isopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 115-119°C.

- 10 Elemental analysis for  $\text{C}_{27}\text{H}_{28}\text{N}_2\text{O}_4\text{Cl}_2$

Calculated: C, 62.92; H, 5.48; N, 5.43.

Found: C, 63.10; H, 5.30; N, 5.76.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.85 (6H, d,  $J=6.4$  Hz), 1.00 (3H, t,  $J=7.2$  Hz), 1.38-1.63 (5H, m), 1.78-1.92 (2H, m), 3.99

- 15 (2H, t,  $J=6.8$  Hz), 4.07-4.15 (2H, m), 5.02 (2H, s), 7.73-7.90 (5H, m), 8.48 (1H, s).

(7) Tert-butyl (4-butoxy-6,7-dichloro-2-isopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1

- 20 (6))

Melting point 129-129.5°C.

Elemental analysis for  $\text{C}_{24}\text{H}_{34}\text{N}_2\text{O}_4\text{Cl}_2$

Calculated: C, 59.38; H, 7.06; N, 5.77.

Found: C, 59.48; H, 7.32; N, 5.80.

- 25  $^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.99 (6H, d,  $J=6.6$  Hz), 1.04 (3H, t,  $J=7.3$  Hz), 1.47 (9H, s), 1.52-1.69 (4H, m), 1.73-1.93 (3H, m), 3.83 (2H, t,  $J=6.5$  Hz), 4.06-4.14 (2H, m), 4.47 (2H, d,  $J=6.4$  Hz), 4.72 (1H, bs), 7.75 (1H, s), 8.47 (1H, s).

- 30 (8) 3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-isopentyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 251-253°C.

- 35 Elemental analysis for  $\text{C}_{19}\text{H}_{27}\text{N}_2\text{O}_2\text{Cl}_3$

Calculated: C, 54.10; H, 6.45; N, 6.64.

Found: C, 54.13; H, 6.44; N, 6.64.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ:0.96 (6H, d, J=6.6 Hz), 1.00 (3H, t, J=7.3 Hz), 1.42-1.92 (7H, m), 3.94 (2H, t, J=6.6 Hz), 4.05-4.13 (4H, m), 7.91 (1H, s), 8.38 (1H, s), 8.79 (3H, bs).

#### Example 34

3-(Aminomethyl)-6,7-dichloro-4-isobutoxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 6,7-dichloro-4-isobutoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.93 (9H, s), 1.08 (6H, d, J=6.6 Hz), 1.43 (3H, t, J=7.1 Hz), 2.04-2.19 (1H, m), 3.70 (2H, d, J=6.6 Hz), 4.04 (2H, bs), 4.42 (2H, q, J=7.1 Hz), 7.83 (1H, s), 8.51 (1H, s).

(2) 6,7-Dichloro-4-isobutoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 156-157°C.

Elemental analysis for C<sub>19</sub>H<sub>23</sub>NO<sub>4</sub>Cl<sub>2</sub>

Calculated: C, 57.01; H, 5.79; N, 3.50.

Found: C, 57.14; H, 5.55; N, 3.58.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.93 (9H, s), 1.10 (6H, d, J=6.6 Hz), 2.11-2.24 (1H, m), 3.78 (2H, d, J=6.2 Hz), 4.21 (2H, bs), 7.76 (1H, s), 8.43 (1H, s).

(3) 6,7-Dichloro-3-hydroxymethyl-4-isobutoxy-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

Melting point 180-180.5°C.

Elemental analysis for C<sub>19</sub>H<sub>25</sub>NO<sub>3</sub>Cl<sub>2</sub> 1/2H<sub>2</sub>O

Calculated: C, 58.39; H, 6.58; N, 3.58.

Found: C, 58.52; H, 6.68; N, 3.57.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.94 (9H, s), 1.16 (6H, d, J=6.6 Hz), 2.12-2.29 (1H, m), 3.09 (1H, bs), 3.67 (2H, d, J=6.2 Hz),

4.21 (2H, bs), 4.83 (2H, bs), 7.67-7.68 (1H, m), 8.22-8.26 (1H, m).

(4) 3-Chloromethyl-6,7-dichloro-4-isobutoxy-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.98 (9H, s), 1.15 (6H, d,  $J=6.6$  Hz), 2.15-2.25 (1H, m), 3.71 (2H, d,  $J=6.2$  Hz), 4.19 (2H, bs), 4.85 (2H, bs), 7.81 (1H, s), 8.50 (1H, s).

(5) 2-(6,7-Dichloro-1-oxo-4-isobutoxy-2-neopentyl-1,2-dihydro-3-isoquinolinyl)methyl-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 147-148°C.

Elemental analysis for  $\text{C}_{27}\text{H}_{28}\text{N}_2\text{O}_4\text{Cl}_2$

Calculated: C, 62.92; H, 5.48; N, 5.43.

Found: C, 62.85; H, 5.59; N, 5.42.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 1.00 (9H, s), 1.11 (6H, d,  $J=6.6$  Hz), 2.17-2.31 (1H, m), 3.76 (2H, d,  $J=6.6$  Hz), 4.03 (2H, bs), 5.05 (2H, s), 7.71-7.84 (5H, m), 8.47 (1H, s).

(6) Tert-butyl (6,7-dichloro-4-isobutoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

Melting point 171-172°C.

Elemental analysis for  $\text{C}_{24}\text{H}_{34}\text{N}_2\text{O}_4\text{Cl}_2$

Calculated: C, 59.38; H, 7.06; N, 5.77.

Found: C, 59.49; H, 6.96; N, 5.91.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.98 (9H, s), 1.13 (6H, d,  $J=6.6$  Hz), 1.46 (9H, s), 2.13-2.27 (1H, m), 3.61 (2H, d,  $J=6.2$  Hz), 4.12 (2H, bs), 4.54 (2H, d,  $J=5.4$  Hz), 4.77 (1H, bs), 7.76 (1H, s), 8.45 (1H, s).

(7) 3-(Aminomethyl)-6,7-dichloro-4-isobutoxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 254-256°C.

Elemental analysis for  $C_{19}H_{27}N_2O_2Cl_3$

Calculated: C, 54.10; H, 6.45; N, 6.64.

Found: C, 53.76; H, 6.40; N, 6.47.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.91 (9H, s), 1.10 (6H, d,  $J=6.6$  Hz),  
5 2.14-2.27 (1H, m), 3.73 (2H, d,  $J=6.6$  Hz), 4.11 (2H, bs),  
4.24 (2H, s), 7.89 (1H, s), 8.38 (1H, s), 8.63 (3H, bs).

**Example 35**

3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-[3-oxo-(1-  
pyrrolidinyl)propyl]-1(2H)-isoquinolinone hydrochloride  
10 (1) tert-butyl 6,7-dichloro-2-(3-ethoxy-3-oxopropyl)-4-  
hydroxy-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate  
(synthesized according to the method similar to that in  
Example 1 (1))

Melting point 114-115°C.

15 Elemental analysis for  $C_{19}H_{21}NO_6Cl_2$

Calculated: C, 53.04; H, 4.92; N, 3.26.

Found: C, 53.04; H, 4.94; N, 3.16.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.24 (3H, t,  $J=7.2$  Hz), 1.66 (9H, s),  
2.86-2.93 (2H, m), 4.15 (2H, q,  $J=7.2$  Hz), 4.39-4.47 (2H,  
20 m), 8.22 (1H, s), 8.49 (1H, s), 11.30 (1H, s).

(2) Tert-butyl 4-butoxy-6,7-dichloro-2-(3-ethoxy-3-  
oxopropyl)-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate  
(synthesized according to the method similar to that in  
Example 1 (2))

25 Melting point 89-90°C.

Elemental analysis for  $C_{23}H_{29}NO_6Cl_2$

Calculated: C, 56.80; H, 6.01; N, 2.88.

Found: C, 56.84; H, 5.93; N, 2.92.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.01 (3H, t,  $J=7.4$  Hz), 1.26 (3H, t,  
30  $J=7.1$  Hz), 1.48-1.61 (2H, m), 1.64 (9H, s), 1.74-1.85  
(2H, m), 2.82-2.90 (2H, m), 3.95 (2H, t,  $J=6.4$  Hz),  
4.12-4.22 (4H, m), 7.80 (1H, s), 8.48 (1H, s).

(3) A solution of tert-butyl 4-butoxy-6,7-dichloro-2-(3-  
ethoxy-3-oxopropyl)-1-oxo-1,2-dihydro-3-

35 isoquinolinecarboxylate (2.43 g, 5 mmol) in  
trifluoroacetic acid (10 ml) was stirred at room



temperature for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was recrystallized from ethyl acetate - diisopropyl ether to give 4-butoxy-6,7-dichloro-2-(3-ethoxy-3-oxopropyl)-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (2.06 g, 95.8%) as crystals.

Melting point 117.5-118°C.

Elemental analysis for  $C_{19}H_{21}NO_6Cl_2$

Calculated: C, 53.04; H, 4.92; N, 3.26.

10 Found: C, 53.20; H, 4.83; N, 3.30.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.00 (3H, t,  $J=7.3$  Hz), 1.24 (3H, t,  $J=7.2$  Hz), 1.44-1.63 (2H, m), 1.75-1.89 (2H, m), 2.96 (2H, t,  $J=7.3$  Hz), 4.00 (2H, t,  $J=6.4$  Hz), 4.15 (2H, t,  $J=7.2$  Hz), 4.30 (2H, t,  $J=7.2$  Hz), 5.01 (1H, bs), 7.83 (1H, s), 8.50 (1H, s).

(4) Ethyl 3-[4-butoxy-6,7-dichloro-3-hydroxymethyl-1-oxo-2(1H)-isoquinolinyl]propionate (synthesized according to the method similar to that in Example 4 (4))

20 Melting point 122-123°C.

Elemental analysis for  $C_{19}H_{23}NO_5Cl_2$

Calculated: C, 54.82; H, 5.57; N, 3.36.

Found: C, 54.71; H, 5.51; N, 3.37.

25  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.03 (3H, t,  $J=7.4$  Hz), 1.23 (3H, t,  $J=7.2$  Hz), 1.49-1.67 (2H, m), 1.78-1.92 (2H, m), 2.82 (1H, bs), 2.92 (2H, t,  $J=6.9$  Hz), 3.89 (2H, t,  $J=6.4$  Hz), 4.13 (2H, q,  $J=7.2$  Hz), 4.43 (2H, t,  $J=6.9$  Hz), 4.86 (2H, s), 7.78 (1H, s), 8.44 (1H, s).

(5) Ethyl 3-[4-butoxy-3-chloromethyl-6,7-dichloro-1-oxo-2(1H)-isoquinolinyl]propionate (synthesized according to the method similar to that in Example 4 (5))

30  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.05 (3H, t,  $J=7.1$  Hz), 1.22 (3H, t,  $J=7.0$  Hz), 1.51-1.66 (2H, m), 1.70-1.95 (2H, m), 2.89 (2H, t,  $J=6.8$  Hz), 3.96 (2H, t,  $J=6.6$  Hz), 4.11 (2H, q,  $J=7.0$  Hz), 4.42 (2H, t,  $J=6.8$  Hz), 4.95 (2H, s), 7.81 (1H, s), 8.49 (1H, s).

(6) Ethyl 3-[4-butoxy-6,7-dichloro-3-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-1-oxo-2(1H)-isoquinolinyl]propionate  
Melting point 167-169°C.

5 Elemental analysis for  $C_{27}H_{26}N_2O_6Cl_2$

Calculated: C, 59.46; H, 4.80; N, 5.14.

Found: C, 59.54; H, 4.66; N, 5.11.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.00 (3H, t,  $J=7.1$  Hz), 1.19 (3H, t,  $J=7.1$  Hz), 1.47-1.61 (2H, m), 1.78-1.93 (2H, m), 2.77

10 (2H, t,  $J=7.0$  Hz), 3.97 (2H, t,  $J=6.7$  Hz), 4.07 (2H, q,  $J=7.1$  Hz), 4.39 (2H, t,  $J=7.0$  Hz), 5.13 (2H, s), 7.72-7.87 (5H, m), 8.47 (1H, s).

(7) A mixture of ethyl 3-[4-butoxy-6,7-dichloro-3-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-1-oxo-2(1H)-

15 isoquinolinyl]propionate (1.36 g, 2.5 mmol) in 6N hydrochloric acid (15 ml) and acetic acid (15 ml) was refluxed with stirring for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was recrystallized from tetrahydrofuran - diisopropyl  
20 ether to give 3-[4-butoxy-6,7-dichloro-3-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-1-oxo-2(1H)-isoquinolinyl]propionic acid (1.08 g, 83.7%) as crystals.  
Melting point 196-197°C.

Elemental analysis for  $C_{26}H_{22}N_2O_6Cl_2 \cdot 2H_2O$

25 Calculated: C, 54.26; H, 4.74; N, 5.06.

Found: C, 54.32; H, 4.38; N, 5.13.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (3H, t,  $J=7.1$  Hz), 1.42-1.60 (2H, m), 1.77-1.91 (2H, m), 2.76 (2H, t,  $J=7.1$  Hz), 3.94 (2H, t,  $J=6.8$  Hz), 4.41 (2H, t,  $J=7.1$  Hz), 5.13 (2H, s),

30 7.73-7.86 (5H, m), 8.44 (1H, s).

(8) A solution of 3-[4-butoxy-6,7-dichloro-3-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-1-oxo-2(1H)-isoquinolinyl]propionic acid (1.03 g, 2.4 mmol),  
pyrrolidine (0.20 ml, 2.4 mmol), 1-ethyl-3-(3-

35 dimethylaminopropyl)carbodiimide hydrochloride (0.46 g, 2.4 mmol) and 1-hydroxybenzotriazole (0.37 g, 2.4 mmol)

in N,N-dimethylformamide (10 ml) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from tetrahydrofuran - diisopropyl ether to give 2-[[4-butoxy-6,7-dichloro-1-oxo-2-[3-oxo-3-(1-pyrrolidinyl)propyl]-1,2-dihydro-3-isoquinolinyl]-methyl]-1H-isoindole-1,3(2H)-dione (0.72 g, 66.1%) as crystals.

Melting point 222-222.5°C.

Elemental analysis for  $C_{29}H_{29}N_3O_5Cl_2$

Calculated: C, 61.01; H, 5.12; N, 7.37.

Found: C, 60.91; H, 5.16; N, 7.21.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.98 (3H, t, J=7.1 Hz), 1.41-1.59 (2H, m), 1.74-1.92 (6H, m), 2.78 (2H, t, J=7.0 Hz), 3.25-3.38 (4H, m), 3.94 (2H, t, J=6.8 Hz), 4.46 (2H, t, J=7.0 Hz), 5.23 (2H, s), 7.70-7.85 (5H, m), 8.47 (1H, s).

(9) Tert-butyl {4-butoxy-6,7-dichloro-1-oxo-{3-oxo-3-(1-pyrrolidinyl)propyl}-1,2-dihydro-3-isoquinolinyl}-methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

Melting point 215-217°C.

Elemental analysis for  $C_{26}H_{35}N_3O_5Cl_2$

Calculated: C, 57.78; H, 6.53; N, 7.77.

Found: C, 57.95; H, 6.43; N, 7.60.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.03 (3H, t, J=7.3 Hz), 1.44 (9H, s), 1.51-1.62 (2H, m), 1.79-1.95 (6H, m), 2.86 (2H, t, J=6.8 Hz), 3.36-3.45 (4H, m), 3.88 (2H, t, J=6.6 Hz), 4.73 (2H, t, J=6.8 Hz), 4.60 (2H, d, J=5.4 Hz), 5.80 (1H, bs), 7.79 (1H, s), 8.45 (1H, s).

(10) 3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-{3-oxo-(1-pyrrolidinyl)propyl}-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 206-206.5°C.

Elemental analysis for  $C_{21}H_{28}N_3O_3Cl_3 \cdot 3/2H_2O$

Calculated: C, 50.06; H, 6.20; N, 8.34.

Found: C, 49.72; H, 6.02; N, 8.23.

- 5  $^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.99 (3H, d, J=7.4 Hz), 1.45-1.63 (2H, m), 1.71-1.88 (6H, m), 2.76 (2H, t, J=6.6 Hz), 3.23-3.38 (4H, m), 3.93 (2H, t, J=6.4 Hz), 4.21-4.28 (4H, m), 7.91 (1H, s), 8.36 (1H, s), 8.79 (3H, bs).

**Example 36**

- 10 3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-methyl-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 4-butoxy-6,7-dichloro-4-hydroxy-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1

- 15 (1))

Melting point 78-80°C.

Elemental analysis for  $C_{17}H_{19}NO_6Cl_2 \cdot 1/4H_2O$

Calculated: C, 54.20; H, 5.22; N, 3.72.

Found: C, 54.16; H, 5.06; N, 3.61.

- 20  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.01 (3H, t, J=7.1 Hz), 1.44 (3H, t, J=7.2 Hz), 1.47-1.58 (2H, m), 1.72-1.86 (2H, m), 3.51 (3H, s), 3.95 (2H, t, J=6.5 Hz), 4.47 (2H, q, J=7.2 Hz), 7.82 (1H, s), 8.51 (1H, s).

- (2) 4-Butoxy-6,7-dichloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

- 25 Melting point 209-210°C.

Elemental analysis for  $C_{15}H_{15}NO_4Cl_2$

Calculated: C, 52.34; H, 4.39; N, 4.07.

- 30 Found: C, 52.21; H, 4.27; N, 3.78.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.01 (3H, t, J=7.3 Hz), 1.49-1.60 (2H, m), 1.74-1.84 (2H, m), 3.58 (3H, s), 3.99 (2H, t, J=6.6 Hz), 5.03 (1H, bs), 7.83 (1H, s), 8.49 (1H, s).

- (3) 4-Butoxy-6,7-dichloro-3-hydroxymethyl-2-methyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

Melting point 146-147°C.

Elemental analysis for  $C_{15}H_{17}NO_3Cl_2$

Calculated: C, 54.56; H, 5.19; N, 4.24.

Found: C, 54.32; H, 4.98; N, 4.14.

5  $^1H$ -NMR( $CDCl_3$ )  $\delta$ :1.04 (3H, t,  $J=7.3$  Hz), 1.44-1.67 (2H, m), 1.77-1.91 (2H, m), 2.52 (1H, bs), 3.71 (3H, s), 3.83 (2H, t,  $J=6.6$  Hz), 4.79 (2H, s), 7.66 (1H, s), 8.38 (1H, s).

(4) 4-Butoxy-3-chloromethyl-6,7-dichloro-2-methyl-1(2H)-  
10 isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

$^1H$ -NMR( $CDCl_3$ )  $\delta$ :1.05 (3H, t,  $J=7.1$  Hz), 1.52-1.76 (2H, m), 1.82-1.96 (2H, m), 3.72 (3H, s), 3.97 (2H, t,  $J=6.5$  Hz), 4.77 (2H, s), 7.81 (1H, s), 8.51 (1H, s).

15 (5) 2-[(4-Butoxy-6,7-dichloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 228-228.5°C.

20 Elemental analysis for  $C_{23}H_{20}N_2O_4Cl_2$

Calculated: C, 60.14; H, 4.39; N, 6.10.

Found: C, 59.92; H, 4.35; N, 6.13.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ :1.01 (3H, t,  $J=7.2$  Hz), 1.46-1.64 (2H, m), 1.80-1.94 (2H, m), 3.56 (3H, s), 4.03 (2H, t,  $J=6.8$  Hz), 5.06 (2H, s), 7.73-7.88 (5H, m), 8.48 (1H, s).

25 (6) Tert-butyl (4-butoxy-6,7-dichloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

30 Melting point 159.5-160°C.

Elemental analysis for  $C_{20}H_{26}N_2O_4Cl_2$

Calculated: C, 55.95; H, 6.10; N, 6.52.

Found: C, 55.93; H, 6.18; N, 6.29.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ :1.04 (3H, t,  $J=7.1$  Hz), 1.47 (9H, s),  
35 1.49-1.63 (2H, m), 1.73-1.93 (2H, m), 3.62 (3H, s), 3.83 (2H, t,  $J=6.6$  Hz), 4.52 (2H, d,  $J=5.4$  Hz), 4.82 (1H, bs),

7.75 (1H, s), 8.46 (1H, s).

(7) 3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-methyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1

5 (7))

Melting point 251-252°C.

Elemental analysis for  $C_{15}H_{19}N_2O_2Cl_3 \cdot 1/4H_2O$

Calculated: C, 48.67; H, 5.31; N, 7.57.

Found: C, 48.69; H, 5.37; N, 7.79.

10  $^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.99 (3H, t,  $J=7.3$  Hz), 1.45-1.63 (2H, m), 1.77-1.91 (2H, m), 3.61 (3H, s), 3.92 (2H, t,  $J=6.4$  Hz), 4.23 (2H, s), 7.91 (1H, s), 8.36 (1H, s), 8.79 (3H, bs).

### Example 37

15 3-(1-Aminoethyl)-4-butoxy-6,7-dichloro-2-methyl-1(2H)-isoquinolinone hydrochloride

(1) To a solution of dimethyl sulfoxide (1.7 ml, 24 mmol) in tetrahydrofuran (10 mmol) was added oxalyl chloride (1.05 ml, 12 mmol) at -78°C and the obtained mixture was stirred at -78°C for 15 min. To the mixture was added 4-butoxy-6,7-dichloro-3-hydroxymethyl-2-methyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 36 (3)) (2.43 g, 5 mmol) and the obtained mixture was stirred at -78°C for 25 5 min. To the mixture was added triethylamine (5.6 ml, 40 mmol) and the obtained mixture was stirred at room temperature for 30 min. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous 30 magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from tetrahydrofuran - diisopropyl ether to give 4-butoxy-6,7-dichloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinealdehyde (2.14 g, 81.7%) as crystals.

35 Melting point 114-115°C.

Elemental analysis for  $C_{15}H_{15}NO_3Cl_2$

Calculated: C, 54.90; H, 4.61; N, 4.27.

Found: C, 54.71; H, 4.39; N, 4.21.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:1.04 (3H, t, J=7.3 Hz), 1.49-1.68 (2H, m), 1.84-1.98 (2H, m), 3.82 (3H, s), 4.05 (2H, t, J=6.6 Hz), 7.96 (2H, s), 8.56 (1H, s), 10.24 (1H, s).

(2) To a solution of 4-butoxy-6,7-dichloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinealdehyde (0.98 g, 24 mmol) in tetrahydrofuran (20 mmol) was added 3N methylmagnesium bromide tetrahydrofuran solution (1.5 ml, 4.5 mmol) at 0°C and the obtained mixture was stirred at 0°C for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate - n-hexane to give 4-butoxy-6,7-dichloro-3-(1-hydroxyethyl)-2-methyl-1(2H)-isoquinolinone (0.95 g, 92.2%) as crystals. Melting point 123-123.5°C.

Elemental analysis for C<sub>16</sub>H<sub>19</sub>NO<sub>3</sub>Cl<sub>2</sub>

Calculated: C, 55.83; H, 5.56; N, 4.07.

Found: C, 55.81; H, 5.59; N, 3.86.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:1.04 (3H, t, J=7.3 Hz), 1.49-1.63 (2H, m), 1.64 (3H, d, J=7.0 Hz), 1.78-1.92 (2H, m), 3.26 (1H, bs), 3.70-3.84 (5H, m), 5.63 (1H, q, J=7.0 Hz), 7.59 (1H, s), 8.36 (1H, s).

(3) 4-Butoxy-3-(1-chloroethyl)-6,7-dichloro-2-methyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:1.05 (3H, t, J=7.3 Hz), 1.51-1.69 (2H, m), 1.82-1.92 (2H, m), 1.96 (3H, d, J=7.2 Hz), 3.83 (3H, s), 3.88-3.96 (2H, m), 5.92-6.00 (1H, m), 7.81 (1H, s), 8.50 (1H, s).

(4) 2-[1-(4-Butoxy-6,7-dichloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)ethyl]-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Elemental analysis for  $C_{24}H_{22}N_2O_4Cl_2$

Calculated: C, 60.90; H, 4.68; N, 5.92.

Found: C, 60.76; H, 4.38; N, 5.72.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (3H, t,  $J=7.3$  Hz), 1.41-1.52 (2H, m), 1.77-1.87 (2H, m), 2.08 (3H, d,  $J=7.6$  Hz), 3.67 (3H, s), 3.84-3.95 (1H, m), 4.05-4.16 (1H, m), 5.81 (1H, q,  $J=7.6$  Hz), 7.72-7.87 (5H, m), 8.47 (1H, s).

(5) Tert-butyl 1-(4-butoxy-6,7-dichloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)ethylcarbamate (synthesized according to the method similar to that in Example 1 (6)).

Melting point 118-118.5°C.

Elemental analysis for  $C_{24}H_{28}N_2O_4Cl_2$

Calculated: C, 56.89; H, 6.37; N, 6.32.

Found: C, 57.11; H, 6.58; N, 6.13.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.04 (3H, t,  $J=7.4$  Hz), 1.43 (9H, s), 1.54 (3H, d,  $J=7.0$  Hz), 1.56-1.74 (2H, m), 1.84-1.98 (2H, m), 3.73 (3H, s), 3.82-4.03 (2H, m), 5.20-5.29 (1H, m), 5.57 (1H, bs), 7.72 (1H, s), 8.48 (1H, s).

(6) 3-(1-Aminoethyl)-4-butoxy-6,7-dichloro-2-methyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7)).

Melting point 224-225°C.

Elemental analysis for  $C_{16}H_{21}N_2O_2Cl_2$

Calculated: C, 50.61; H, 5.57; N, 7.38.

Found: C, 50.38; H, 5.63; N, 7.28.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.99 (3H, t,  $J=7.3$  Hz), 1.44-1.62 (2H, m), 1.69 (3H, d,  $J=7.4$  Hz), 1.81-1.92 (2H, m), 3.61 (3H, s), 3.92 (2H, t,  $J=6.8$  Hz), 4.95 (2H, bs), 7.87 (1H, s), 8.36 (1H, s), 8.87 (3H, bs).

#### Example 38

3-(1-Aminobutyl)-4-butoxy-6,7-dichloro-2-methyl-1(2H)-isoquinolinone hydrochloride

(1) 4-Butoxy-6,7-dichloro-3-(1-hydroxybutyl)-2-methyl-1(2H)-isoquinolinone (synthesized according to the



method similar to that in Example 37 (2))

Melting point 105.5-106°C.

Elemental analysis for  $C_{18}H_{23}NO_3Cl_2$

Calculated: C, 58.07; H, 6.23; N, 3.76.

5 Found: C, 58.09; H, 6.53; N, 3.57.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.00 (3H, t,  $J=7.3$  Hz), 1.04 (3H, t,  $J=7.3$  Hz), 1.31-2.10 (8H, m), 2.98 (1H, bs), 3.75 (3H, s), 3.82 (2H, t,  $J=6.4$  Hz), 5.31-5.40 (1H, m), 7.66 (1H, s), 8.41 (1H, s).

10 (2) 4-Butoxy-3-(1-chlorobutyl)-6,7-dichloro-2-methyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.97 (3H, t,  $J=7.4$  Hz), 1.05 (3H, t,  $J=7.3$  Hz), 1.22-1.76 (4H, m), 1.80-1.95 (2H, m), 2.17-2.35 (2H, m), 3.79 (3H, s), 3.91 (2H, t,  $J=6.2$  Hz), 5.79 (1H, bs), 7.81 (1H, s), 8.50 (1H, s).

15 (3) 2-[1-(4-Butoxy-6,7-dichloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)butyl]-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Elemental analysis for  $C_{26}H_{26}N_2O_4Cl_2$

Calculated: C, 62.28; H, 5.23; N, 5.59.

Found: C, 62.05; H, 5.02; N, 5.60.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.00 (3H, t,  $J=7.2$  Hz), 1.03 (3H, t,  $J=7.2$  Hz), 1.37-1.62 (4H, m), 1.78-1.91 (2H, m), 1.99-2.17 (1H, m), 2.89-3.08 (1H, m), 3.65 (3H, s), 3.75-3.93 (1H, m), 4.08-4.19 (1H, m), 5.64-5.72 (1H, m), 7.70-7.90 (5H, m), 8.47 (1H, s).

25 (4) Tert-butyl 1-(4-butoxy-6,7-dichloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)butylcarbamate (synthesized according to the method similar to that in Example 1 (6))

Elemental analysis for  $C_{23}H_{32}N_2O_4Cl_2$

Calculated: C, 58.60; H, 6.84; N, 5.94.

35 Found: C, 58.67; H, 6.62; N, 5.82.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.87 (3H, t,  $J=7.1$  Hz), 1.07 (3H, t,

J=7.4 Hz), 1.43 (9H, s), 1.44-1.98 (8H, m), 3.74 (3H, s), 3.82-3.97 (2H, m), 5.12 (1H, bs), 5.37 (1H, bs), 7.71 (1H, s), 8.48 (1H, s).

(5) 3-(1-Aminobutyl)-4-butoxy-6,7-dichloro-2-methyl-1(2H)-isoquinoline hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 217-218°C.

Elemental analysis for  $C_{18}H_{25}N_2O_2Cl_3 \cdot 1/2H_2O$

Calculated: C, 51.87; H, 6.29; N, 6.72

10 Found: C, 51.66; H, 6.44; N, 6.62.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.92 (3H, t, J=7.4 Hz), 0.99 (3H, t, J=7.4 Hz), 1.26-1.59 (4H, m), 1.83-2.21 (4H, m), 3.59 (3H, s), 3.82-3.93 (2H, m), 4.88 (1H, bs), 7.88 (1H, s), 8.36 (1H, s), 9.06 (3H, bs).

15 **Example 39**

3-(1-Amino-3-methylbutyl)-4-butoxy-6,7-dichloro-2-methyl-1(2H)-isoquinolinone hydrochloride

(1) 4-Butoxy-6,7-dichloro-3-(1-hydroxy-3-methylbutyl)-2-methyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 37 (2))

Melting point 121-122°C.

Elemental analysis for  $C_{19}H_{25}NO_3Cl_2$

Calculated: C, 59.07; H, 6.52; N, 3.63.

Found: C, 59.13; H, 6.54; N, 3.51.

25  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.02 (6H, d, J=6.6 Hz), 1.04 (3H, t, J=7.4 Hz), 1.50-1.67 (3H, m), 1.79-2.04 (4H, m), 2.90 (1H, bs), 3.74 (3H, s), 3.77-3.89 (2H, m), 5.39-5.46 (1H, m), 7.66 (1H, s), 8.41 (1H, s).

(2) 4-Butoxy-3-(1-chloro-3-methylbutyl)-6,7-dichloro-2-methyl-1(2H)-isoquinoline (synthesized according to the method similar to that in Example 4 (5))

30  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.95 (3H, d, J=6.6 Hz), 0.97 (3H, d, J=6.6 Hz), 1.05 (3H, t, J=7.3 Hz), 1.52-1.99 (5H, m), 2.13-2.26 (2H, m), 3.79 (3H, s), 3.93 (2H, t, J=6.6 Hz), 5.90 (1H, bs), 7.81 (1H, s), 8.50 (1H, s).

(3) 2-[1-(4-Butoxy-6,7-dichloro-2-methyl-1-oxo-1,2-

dihydro-3-isoquinolinyl)-3-methylbutyl]-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Elemental analysis for  $C_{27}H_{28}N_2O_4Cl_2$

5 Calculated: C, 62.69; H, 5.48; N, 5.43.

Found: C, 62.92; H, 5.29; N, 5.39.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.81-1.07 (9H, m), 1.40-1.54 (2H, m), 1.63-1.92 (4H, m), 3.03-3.15 (1H, m), 3.72 (3H, s), 3.79-3.90 (1H, m), 4.07-4.19 (1H, m), 5.74-5.82 (1H, m), 10 7.72-7.85 (5H, m), 8.47 (1H, s).

(4) Tert-butyl 1-(4-butoxy-6,7-dichloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)-3-methylbutylcarbamate (synthesized according to the method similar to that in Example 1 (6))

15 Elemental analysis for  $C_{24}H_{34}N_2O_4Cl_2$

Calculated: C, 59.38; H, 7.06; N, 5.77.

Found: C, 59.31; H, 6.96; N, 5.53.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (3H, d, J=6.6 Hz), 1.01 (3H, d, J=6.6 Hz), 1.06 (3H, t, J=7.4 Hz), 1.43 (9H, s), 1.46- 20 1.69 (4H, m), 1.74-1.95 (3H, m), 3.73 (3H, s), 3.83-3.98 (2H, m), 5.21 (1H, bs), 5.31 (1H, bs), 7.71 (1H, s), 8.48 (1H, s).

(5) 3-(1-Amino-3-methylbutyl)-4-butoxy-6,7-dichloro-2-methyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 212.5-213.5°C.

Elemental analysis for  $C_{19}H_{27}N_2O_2Cl_3$

Calculated: C, 54.10; H, 6.45; N, 6.64.

30 Found: C, 53.92; H, 6.55; N, 6.47.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.93-0.97 (6H, m), 0.99 (3H, t, J=7.4 Hz), 1.42-2.18 (7H, m), 3.59 (3H, s), 3.89 (2H, bs), 5.05 (1H, bs), 7.89 (1H, s), 8.36 (1H, s), 9.18 (3H, bs).

Example 40

35 3-(1-Aminohexyl)-4-butoxy-6,7-dichloro-2-methyl-1(2H)-isoquinolinone hydrochloride

(1) 4-Butoxy-6,7-dichloro-3-(1-hydroxyhexyl)-2-methyl-1(2H)-isoquinoline (synthesized according to the method similar to that in Example 37 (2))

Melting point 95-96°C.

5 Elemental analysis for  $C_{20}H_{27}NO_3Cl_2$

Calculated: C, 60.00; H, 6.80; N, 3.50.

Found: C, 59.90; H, 6.75; N, 3.45.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.87-0.93 (3H, m), 1.04 (3H, t,  $J=7.2$  Hz), 1.33-1.35 (4H, m), 1.49-2.05 (8H, m), 2.99 (1H, bs),  
10 3.74 (3H, s), 3.81 (2H, t,  $J=6.4$  Hz), 5.28-5.38 (1H, m), 7.64 (1H, s), 8.40 (1H, s).

(2) 4-Butoxy-3-(1-chlorohexyl)-6,7-dichloro-2-methyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

15  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.82-0.91 (3H, m), 1.05 (3H, t,  $J=7.3$  Hz), 1.22-1.39 (6H, m), 1.51-1.76 (4H, m), 1.80-1.95 (2H, m), 3.79 (3H, s), 3.91 (2H, t,  $J=6.2$  Hz), 5.78 (1H, bs), 7.81 (1H, s), 8.50 (1H, s).

(3) 2-[1-(4-Butoxy-6,7-dichloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)hexyl]-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Elemental analysis for  $C_{28}H_{30}N_2O_4Cl_2$

Calculated: C, 63.52; H, 5.71; N, 5.29.

25 Found: C, 63.25; H, 5.78; N, 5.03.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.90 (3H, t,  $J=7.0$  Hz), 1.00 (3H, t,  $J=7.3$  Hz), 1.30-1.59 (8H, m), 1.77-1.91 (2H, m), 2.01-2.14 (1H, m), 2.97-3.04 (1H, m), 3.70 (3H, s), 3.80-3.92 (1H, m), 4.07-4.18 (1H, m), 5.61-5.69 (1H, m), 7.72-7.85  
30 (5H, m), 8.47 (1H, s).

(4) Tert-butyl 1-(4-butoxy-6,7-dichloro-2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)hexylcarbamate (synthesized according to the method similar to that in Example 1 (6))

35 Elemental analysis for  $C_{25}H_{36}N_2O_4Cl_2$

Calculated: C, 60.12; H, 7.26; N, 5.61.

Found: C, 59.95; H, 7.04; N, 5.53.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.88 (3H, t, J=6.0 Hz), 1.06 (3H, t, J=7.4 Hz), 1.22-1.32 (4H, m), 1.43 (9H, s), 1.50-1.69 (4H, m), 1.74-1.98 (4H, m), 3.73 (3H, s), 3.82-3.96 (2H, m), 5.10-5.12 (1H, m), 5.37 (1H, bs), 7.71 (1H, s), 8.48 (1H, s).

(5) 3-(1-Aminohexyl)-4-butoxy-6,7-dichloro-2-methyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 199.5-200°C.

Elemental analysis for C<sub>20</sub>H<sub>29</sub>N<sub>2</sub>O<sub>2</sub>Cl<sub>3</sub> 1/2H<sub>2</sub>O

Calculated: C, 54.00; H, 6.80; N, 6.30.

Found: C, 54.18; H, 6.87; N, 6.14.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ:0.85-0.88 (3H, m), 0.99 (3H, t, J=7.3 Hz), 1.26-1.62 (7H, m), 1.83-2.18 (4H, m), 3.59 (3H, s), 3.81-3.92 (2H, m), 4.87 (1H, bs), 7.89 (1H, s), 8.36 (1H, s), 9.09 (3H, bs).

#### Example 41

3-[(Aminomethyl)-4-butoxy-6,7-dichloro-1-oxo-2(1H)-isoquinolinyl]-N-isopropylpropanamide hydrochloride (1) 3-[4-Butoxy-6,7-dichloro-3-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-1-oxo-1,2-dihydro-3-isoquinolinyl]-N-isopropylpropanamide (synthesized according to the method similar to that in Example 35 (8)).

Melting point 232-232.5°C.

Elemental analysis for C<sub>28</sub>H<sub>29</sub>N<sub>3</sub>O<sub>5</sub>Cl<sub>2</sub>

Calculated: C, 60.22; H, 5.23; N, 7.52.

Found: C, 59.98; H, 5.48; N, 7.41.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.99 (3H, t, J=7.3 Hz), 1.05 (6H, d, J=6.6 Hz), 1.44-1.59 (2H, m), 1.74-1.91 (2H, m), 2.66 (2H, t, J=6.8 Hz), 3.92 (2H, t, J=6.8 Hz), 3.92-4.02 (1H, m), 4.47 (2H, t, J=7.0 Hz), 5.15 (2H, s), 5.76 (2H, d, J=7.6 Hz), 7.70-7.86 (5H, m), 8.43 (1H, s).

(2) Tert-butyl {4-butoxy-6,7-dichloro-2-{3-

(isopropylamino)-3-oxopropyl}-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

Melting point 221-221.5°C.

5 Elemental analysis for  $C_{25}H_{35}N_3O_5Cl_2$

Calculated: C, 56.82; H, 6.68; N, 7.95.

Found: C, 56.72; H, 6.51; N, 7.93.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.03 (3H, t, J=7.1 Hz), 1.06 (6H, d, J=6.6 Hz), 1.46 (9H, s), 1.51-1.66 (2H, m), 1.74-1.94

10 (2H, m), 2.71 (2H, t, J=7.0 Hz), 3.87 (3H, t, J=6.6 Hz), 3.94-4.08 (1H, m), 4.35 (2H, t, J=7.0 Hz), 4.56 (2H, d, J=5.8 Hz), 5.69 (1H, bs), 6.01 (1H, bs), 7.79 (1H, s),

8.43 (1H, s). (3) 3-[(Aminomethyl)-4-butoxy-6,7-dichloro-1-oxo-2(1H)-

15 isoquinolinyl]-N-isopropylpropanamide hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 189-191°C.

Elemental analysis for  $C_{26}H_{28}N_3O_3Cl_3 \cdot 2H_2O$

20 Calculated: C, 47.96; H, 6.44; N, 8.39.

Found: C, 48.07; H, 6.05; N, 8.36.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.95 (6H, d, J=6.6 Hz), 0.99 (3H, t, J=7.3 Hz), 1.44-1.63 (2H, m), 1.77-1.91 (2H, m), 2.56

(2H, t, J=6.6 Hz), 3.71-3.82 (1H, m), 3.91 (2H, t, J=6.6 Hz), 4.20-4.31 (4H, m), 4.84 (2H, s), 7.92 (1H, s), 8.02

25 (1H, d, J=7.4 Hz), 8.38 (1H, s), 8.75 (3H, bs).

Example 42

3-{3-(Aminomethyl)-4-butoxy-6,7-dichloro-1-oxo-2(1H)-isoquinolinyl}-N-phenylpropanamide hydrochloride

30 (1) 3-[4-Butoxy-6,7-dichloro-3-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-1-oxo-1,2-dihydro-3-

isoquinolinyl]-N-phenylpropanamide (synthesized according to the method similar to that in Example 35 (8))

35 Melting point 204-206°C.

Elemental analysis for  $C_{31}H_{27}N_3O_5Cl_2$

Calculated: C, 62.84; H, 4.59; N, 7.09.

Found: C, 62.46; H, 4.66; N, 7.08.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.97 (3H, t, J=7.3 Hz), 1.38-1.57 (2H, m), 1.78-1.89 (2H, m), 2.88 (2H, t, J=6.8 Hz), 3.87 (2H, t, J=6.8 Hz), 4.57 (2H, t, J=6.6 Hz), 5.16 (2H, s), 7.03-7.10 (1H, m), 7.23-7.31 (2H, m), 7.46-7.51 (2H, m), 7.69-7.85 (5H, m), 8.34 (1H, s), 8.52 (1H, s).

(2) Tert-butyl {2-(2-anilino-3-oxopropyl)-4-butoxy-6,7-dichloro-1-oxo-1,2-dihydro-3-isoquinolinyl}methylcarbamate (synthesized according to the method similar to that in Example 1 (6)).

Melting point 219-220°C.

Elemental analysis for C<sub>28</sub>H<sub>33</sub>N<sub>3</sub>O<sub>5</sub>Cl<sub>2</sub>

Calculated: C, 59.79; H, 5.91; N, 7.47.

Found: C, 59.92; H, 5.84; N, 7.42.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.03 (3H, t, J=7.3 Hz), 1.46 (9H, s), 1.47-1.65 (2H, m), 1.78-1.93 (2H, m), 2.90 (2H, t, J=7.2 Hz), 3.83 (2H, t, J=6.6 Hz), 4.48 (2H, t, J=7.2 Hz), 4.60 (2H, d, J=5.8 Hz), 5.34 (1H, bs), 7.04-7.11 (1H, m), 7.25-7.33 (2H, m), 7.55-7.59 (2H, m), 7.76 (1H, s), 8.41 (1H, s), 8.72 (1H, bs).

(3) 3-{3-(Aminomethyl)-4-butoxy-6,7-dichloro-1-oxo-2(1H)-isoquinolinyl}-N-phenylpropanamide hydrochloride (synthesized according to the method similar to that in Example 1 (7)).

Melting point 243-244°C.

Elemental analysis for C<sub>23</sub>H<sub>26</sub>N<sub>3</sub>O<sub>3</sub>Cl<sub>3</sub>

Calculated: C, 55.38; H, 5.25; N, 8.42.

Found: C, 55.31; H, 5.45; N, 8.27.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.97 (3H, t, J=7.3 Hz), 1.40-1.60 (2H, m), 1.73-1.87 (2H, m), 2.83 (2H, t, J=6.4 Hz), 3.84 (2H, t, J=6.4 Hz), 4.31-4.34 (4H, m), 6.99-7.06 (1H, m), 7.23-7.31 (2H, m), 7.54-7.58 (2H, m), 7.91 (1H, s), 8.40 (1H, s), 8.65 (3H, bs), 10.23 (1H, s).

Example 43

3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-{3-oxo-3-(1,3-

thiazolidin-3-yl)propyl}-1(2H)-isoquinolinone  
hydrochloride

(1) 2-[4-Butoxy-6,7-dichloro-1-oxo-2-{3-oxo-3-(1,3-  
thiazolidin-3-yl)propyl)methyl]-1H-isoindole-1,3(2H)-  
5 dione (synthesized according to the method similar to  
that in Example 35 (8))

Melting point 218-220°C.

Elemental analysis for  $C_{28}H_{27}N_3O_5Cl_2S \cdot 1/4H_2O$

Calculated: C, 56.71; H, 4.67; N, 7.09.

10 Found: C, 56.66; H, 4.58; N, 6.92.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (3H, t,  $J=7.2$  Hz), 1.42-1.60 (2H,  
m), 1.77-1.91 (2H, m), 2.80-2.94 (2H, m), 2.98 (2H, t,  
 $J=6.3$  Hz), 3.60 (1H, t,  $J=6.2$  Hz), 3.72 (1H, t,  $J=6.2$   
Hz), 3.95 (2H, t,  $J=6.3$  Hz), 4.35-4.47 (4H, m), 5.21 (2H,  
15 s), 7.71-7.86 (5H, m), 8.46 (1H, s).

(2) Tert-butyl {4-butoxy-6,7-dichloro-1-oxo-2-{3-oxo-3-  
(1,3-thiazolidin-3-yl)propyl}-1,2-dihydro-3-  
isoquinolinyl)methylcarbamate (synthesized according to  
the method similar to that in Example 1 (6))

20 Melting point 218-218.5°C.

Elemental analysis for  $C_{25}H_{33}N_3O_5Cl_2S$

Calculated: C, 53.71; H, 5.96; N, 7.52.

Found: C, 54.08; H, 6.20; N, 7.35.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.03 (3H, t,  $J=7.3$  Hz), 1.45 (9H, s),  
25 1.51-1.63 (2H, m), 1.80-1.94 (2H, m), 2.89-3.00 (2H, m),  
3.06 (2H, t,  $J=6.2$  Hz), 3.69-3.91 (4H, m), 4.38 (2H, t,  
 $J=6.8$  Hz), 4.46 (1H, s), 4.54 (1H, s), 4.61 (2H, d,  
 $J=5.6$  Hz), 5.40 (1H, bs), 7.79 (1H, s), 8.45 (1H, s).

(3) 3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-{3-oxo-3-  
30 (1,3-thiazolidin-3-yl)propyl}-1(2H)-isoquinolinone  
hydrochloride (synthesized according to the method  
similar to that in Example 1 (7))

Melting point 206-207°C.

Elemental analysis for  $C_{20}H_{26}N_3O_3Cl_2S$

35 Calculated: C, 48.54; H, 5.30; N, 8.49.

Found: C, 48.19; H, 5.19; N, 8.36.



<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ:0.99 (3H, t, J=7.3 Hz), 1.45-1.64 (2H, m), 1.78-1.92 (2H, m), 2.84 (2H, bs), 2.97 (1H, t, J=6.2 Hz), 3.06 (1H, t, J=6.2 Hz), 3.46 (2H, s), 3.65 (2H, q, J=6.2 Hz), 3.93 (2H, t, J=6.4 Hz), 4.27 (2H, d, J=6.6 Hz), 4.44 (1H, s), 4.50 (1H, s), 7.92 (1H, s), 8.38 (1H, s), 8.66 (3H, bs).

#### Example 44

(2S)-1-[3-[3-(Aminomethyl)-4-butoxy-6,7-dichloro-1-oxo-2(1H)-isoquinolinyl]propanoyl]-2-pyrrolidinecarboxamide hydrochloride

(1) (2S)-1-[3-[4-Butoxy-6,7-dichloro-3-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-1-oxo-2(1H)-isoquinolinyl]propanoyl]-2-pyrrolidinecarboxamide (synthesized according to the method similar to that in Example 35. (8))

Melting point 235-236.5°C.

Elemental analysis for C<sub>30</sub>H<sub>30</sub>N<sub>4</sub>O<sub>6</sub>Cl<sub>2</sub> 1/2H<sub>2</sub>O

Calculated: C, 57.88; H, 5.02; N, 9.00.

Found: C, 57.86; H, 4.94; N, 8.90.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:1.00 (3H, t, J=7.3 Hz), 1.43-1.62 (2H, m), 1.69-1.99 (4H, m), 2.33-2.42 (1H, m), 2.67-2.89 (2H, m), 3.22-3.29 (2H, m), 3.98 (2H, t, J=6.6 Hz), 4.35-4.49 (2H, m), 5.16 (2H, d, J=2.2 Hz), 5.37 (1H, bs), 7.06 (1H, bs), 7.72-7.86 (5H, m), 8.44 (1H, s).

(2) Tert-butyl (2-{3-[(2S)-2-(aminocarbonyl)pyrroliziny]-3-oxopropyl}-4-butoxy-6,7-dichloro-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

Melting point 159-160°C.

Elemental analysis for C<sub>26</sub>H<sub>35</sub>N<sub>3</sub>O<sub>5</sub>Cl<sub>2</sub>

Calculated: C, 57.78; H, 6.53; N, 7.77.

Found: C, 57.95; H, 6.43; N, 7.60.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:1.03 (3H, t, J=7.2 Hz), 1.43 (9H, s), 1.53-1.73 (4H, m), 1.83-2.00 (4H, m), 2.33-2.42 (1H, m), 2.79-2.98 (2H, m), 3.37-3.65 (2H, m), 3.87 (2H, t, J=6.5

Hz), 4.24-4.44 (2H, m), 4.55 (2H, d, J=6.4 Hz), 5.34 (1H, bs), 5.41 (1H, bs), 7.13 (1H, bs), 7.79 (1H, s), 8.42 (1H, s).

(3) (2S)-1-[3-[3-(Aminomethyl)-4-butoxy-6,7-dichloro-1-oxo-2(1H)-isoquinolinyl]propanoyl]-2-pyrrolidinecarboxamide hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 185-185.5°C.

10 Elemental analysis for  $C_{22}H_{29}N_4O_4Cl_2 \cdot 1/2H_2O$   
Calculated: C, 49.96; H, 5.72; N, 10.59.

Found: C, 50.12; H, 5.79; N, 10.29.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 1.00 (3H, t, J=7.3 Hz), 1.45-1.64 (2H, m), 1.72-1.99 (5H, m), 2.65-2.83 (2H, m), 3.33-3.55 (4H, m), 3.93 (2H, t, J=6.4 Hz), 4.08-4.28 (4H, m), 6.94 (1H, bs), 7.35 (1H, bs), 7.92 (1H, s), 8.38 (1H, s), 8.72 (3H, bs).

#### Example 45

(2S)-1-[3-[3-(Aminomethyl)-4-butoxy-6,7-dichloro-1-oxo-2(1H)-isoquinolinyl]propanoyl]-2-pyrrolidine carbonitrile hydrochloride

(1) A solution of tert-butyl (2-{3-[3-(2S)-2-(aminocarbonyl)pyrroliziny]-3-oxopropyl}-4-butoxy-6,7-dichloro-1-oxo-1,2-dihydro-3-isoquinolinyl)-methylcarbamate (Example 44 (1)) (0.58 g, 1 mmol) and cyanuric chloride (0.54 g, 3 mmol) in N,N-dimethylformamide (50 mmol) was stirred at 0°C for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from tetrahydrofuran - diisopropyl ether to give tert-butyl (4-butoxy-6,7-dichloro-2-{3-[3-(2S)-2-cyanopyrroliziny]-3-oxopropyl}-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.39 g, 69.6%) as crystals.

Melting point 181-183°C.

Elemental analysis for  $C_{27}H_{34}N_4O_5Cl_2$

Calculated: C, 57.35; H, 6.06; N, 9.91.

Found: C, 57.16; H, 6.24; N, 9.61.

- 5  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.03 (3H, t,  $J=7.4$  Hz), 1.45 (9H, s),  
1.51-1.63 (2H, m), 1.76-1.94 (2H, m), 2.11-2.32 (4H, m),  
2.91 (2H, t,  $J=6.8$  Hz), 3.44-3.51 (1H, m), 3.62-3.67 (1H,  
m), 3.88 (2H, t,  $J=6.6$  Hz), 4.40 (2H, t,  $J=6.8$  Hz), 4.61  
(2H, d,  $J=5.6$  Hz), 4.63-4.72 (1H, m), 5.38 (1H, s), 7.79  
10 (1H, s), 8.44 (1H, s).

(2) (2S)-1-[3-[3-(Aminomethyl)-4-butoxy-6,7-dichloro-1-  
oxo-2(1H)-isoquinolinyl]propanoyl]-2-pyrrolidine  
carbonitrile hydrochloride (synthesized according to the  
method similar to that in Example 1 (7))

- 15  $^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.99 (3H, t,  $J=7.3$  Hz), 1.47-1.64 (2H,  
m), 1.71-2.19 (6H, m), 2.78-2.88 (2H, m), 3.36-3.82 (2H,  
m), 3.93 (2H, t,  $J=6.4$  Hz), 4.16-4.58 (5H, m), 7.93 (1H,  
s), 8.38 (1H, s), 8.64 (3H, bs).

#### Example 46

- 20 3-(Aminomethyl)-4-butoxy-2-neopentyl-1(2H)-  
isoquinolinone hydrochloride

(1) Ethyl 4-hydroxy-2-neopentyl-1-oxo-1,2-dihydro-3-  
isoquinolinecarboxylate (synthesized according to the  
method similar to that in Example 1 (1))

- 25 Melting point 72-72.5°C.

Elemental analysis for  $C_{17}H_{21}NO_4 \cdot 1/4H_2O$

Calculated: C, 66.32; H, 7.04; N, 4.55.

Found: C, 66.40; H, 7.14; N, 4.54.

- $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.85 (9H, s), 1.47 (3H, t,  $J=7.2$  Hz),  
30 4.48 (2H, q,  $J=7.2$  Hz), 4.54 (2H, bs), 7.69-7.80 (2H, m),  
8.13-8.18 (1H, m), 8.44-8.49 (1H, m), 10.85 (1H, s).

(2) Ethyl 4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-  
isoquinolinecarboxylate (synthesized according to the  
method similar to that in Example 1 (2))

- 35  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.94 (9H, s), 1.01 (3H, t,  $J=7.3$  Hz),  
1.44 (3H, t,  $J=7.2$  Hz), 1.44-1.60 (2H, m), 1.74-1.84 (2H,

m), 3.96 (2H, t, J=6.6 Hz), 4.11 (2H, bs), 4.43 (2H, q, J=7.2 Hz), 7.51-7.61 (1H, m), 7.68-7.81 (2H, m), 8.43-8.47 (1H, m).

(3) 4-Butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-

5 isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point: 146-148°C.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.96 (9H, s), 1.00 (3H, t, J=7.4 Hz), 1.46-1.65 (2H, m), 1.76-1.90 (2H, m), 4.01 (2H, t, J=6.6 Hz), 4.19 (2H, bs), 5.71 (1H, bs), 7.51-7.60 (1H, m), 7.67-7.86 (2H, m), 8.41-8.45 (1H, m).

(4) 4-Butoxy-3-hydroxymethyl-2-neopentyl-1(2H)-

isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

15 Melting point: 123-124°C.

Elemental analysis for C<sub>19</sub>H<sub>27</sub>NO<sub>3</sub>

Calculated: C, 70.89; H, 8.61; N, 4.35.

Found: C, 71.29; H, 8.23; N, 4.36.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.00 (9H, s), 1.07 (3H, t, J=7.3 Hz), 1.50-1.68 (2H, m), 1.80-1.94 (2H, m), 2.35 (1H, bs), 3.91 (2H, t, J=6.4 Hz), 4.22 (2H, bs), 4.89 (2H, bs), 7.42-7.50 (1H, m), 7.60-7.72 (2H, m), 8.35 (1H, d, J=8.1 Hz).

(5) 4-Butoxy-3-chloromethyl-2-neopentyl-1(2H)-

25 isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.99 (9H, s), 1.04 (3H, t, J=7.1 Hz), 1.52-1.69 (2H, m), 1.82-1.96 (2H, m), 3.96 (2H, t, J=6.6 Hz), 4.18 (2H, bs), 4.90 (2H, bs), 7.50-7.58 (1H, m), 7.66-7.78 (2H, m), 8.42-8.46 (1H, m).

(6) 2-((4-Butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl)-1H-indole-1,3(2H)-dione

(synthesized according to the method similar to that in Example 4 (6))

35 Melting point 132.5-133°C.

Elemental analysis for C<sub>27</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub> 1/4H<sub>2</sub>O

Calculated: C, 71.90; H, 6.82; N, 6.21.

Found: C, 72.18; H, 6.73; N, 6.12.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.00 (3H, t, J=7.3 Hz), 1.01 (9H, s),  
1.45-1.60 (2H, m), 1.82-1.96 (2H, m), 4.03 (2H, t, J=6.8  
5 Hz), 4.14 (2H, bs), 5.09 (2H, s), 7.46-7.54 (1H, m),  
7.64-7.83 (6H, m), 8.39-8.43 (1H, m).

(7) Tert-butyl (4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-  
3-isoquinolinyl)methylcarbamate (synthesized according  
to the method similar to that in Example 1 (6))

10 Melting point 138-139°C.

Elemental analysis for C<sub>24</sub>H<sub>36</sub>N<sub>2</sub>O<sub>4</sub>

Calculated: C, 69.20; H, 8.71; N, 6.73.

Found: C, 69.30; H, 8.80; N, 6.70.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.00 (9H, s), 1.03 (3H, t, J=7.4 Hz),  
15 1.45 (9H, s), 1.53-1.65 (2H, m), 1.76-1.94 (2H, m), 3.87  
(2H, t, J=6.6 Hz), 4.14 (2H, bs), 4.58 (2H, d, J=5.2 Hz),  
4.66 (1H, bs), 7.46-7.54 (1H, m), 7.64-7.73 (2H, m),  
8.40-8.44 (1H, m).

(8) 3-(Aminomethyl)-4-butoxy-2-neopentyl-1(2H)-  
20 isoquinolinone hydrochloride (synthesized according to  
the method similar to that in Example 1 (7))

Melting point 231-232°C.

Elemental analysis for C<sub>19</sub>H<sub>29</sub>N<sub>2</sub>O<sub>2</sub>Cl

Calculated: C, 64.67; H, 8.28; N, 7.94.

25 Found: C, 64.61; H, 8.44; N, 7.76.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.91 (9H, s), 0.99 (3H, t, J=7.3 Hz),  
1.48-1.62 (2H, m), 1.78-1.92 (2H, m), 3.94 (2H, t, J=6.4  
Hz), 4.11 (2H, bs), 4.25 (2H, bs), 7.58-7.67 (1H, m),  
7.77-7.90 (2H, m), 8.27-8.30 (1H, m), 8.59 (3H, bs).

30 Example 47

3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-(2-furylmethyl)-  
1(2H)-isoquinolinone hydrochloride

(1) Ethyl 6,7-dichloro-2-(2-furylmethyl)-4-hydroxy-1-  
oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized  
35 according to the method similar to that in Example 1  
(1))

Melting point 134-135°C.

Elemental analysis for  $C_{17}H_{13}NO_5Cl_2$

Calculated: C, 53.42; H, 3.43; N, 3.66.

Found: C, 53.84; H, 3.53; N, 3.44.

5  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.42 (3H, t,  $J=7.2$  Hz), 1.42 (2H, q,  $J=7.2$  Hz), 5.68 (2H, s), 6.16 (1H, dd,  $J=0.8, 3.1$  Hz), 6.27 (1H, dd,  $J=2.0, 3.1$  Hz), 7.28 (1H, dd,  $J=0.8, 2.0$  Hz), 8.21 (1H, s), 8.54 (1H, s), 11.11 (1H, s).

(2) Ethyl 4-butoxy-6,7-dichloro-2-(2-furylmethyl)-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))

10  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.00 (3H, t,  $J=7.4$  Hz), 1.37 (3H, t,  $J=7.1$  Hz), 1.42-1.61 (2H, m), 1.71-1.85 (2H, m), 3.92 (2H, t,  $J=6.4$  Hz), 4.39 (2H, q,  $J=7.1$  Hz), 5.36 (2H, s), 6.28-6.32 (2H, m), 7.32 (1H, d,  $J=1.5$  Hz), 7.81 (1H, s), 8.53 (1H, s).

(3) 4-Butoxy-6,7-dichloro-2-(2-furylmethyl)-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 147.5-148°C.

Elemental analysis for  $C_{19}H_{17}NO_5Cl_2$

Calculated: C, 57.59; H, 4.83; N, 3.53.

25 Found: C, 57.40; H, 4.79; N, 3.37.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (3H, t,  $J=7.3$  Hz), 1.47-1.62 (2H, m), 1.75-1.89 (2H, m), 4.00 (2H, t,  $J=6.6$  Hz), 5.16 (1H, bs), 5.52 (2H, s), 6.28 (1H, dd,  $J=1.8, 3.2$  Hz), 6.35 (1H, dd,  $J=0.8, 3.2$  Hz), 7.30 (1H, dd,  $J=0.8, 1.8$  Hz), 7.82 (1H, s), 8.54 (1H, s).

(4) 4-Butoxy-6,7-dichloro-2-(2-furylmethyl)-3-hydroxymethyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

35 Melting point 120-121°C.

Elemental analysis for  $C_{19}H_{19}NO_5Cl_2$

Calculated: C, 57.59; H, 4.83; N, 3.53.

Found: C, 57.40; H, 4.79; N, 3.37.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.04 (3H, t, J=7.3 Hz), 1.49-1.62 (2H, m), 1.78-1.92 (2H, m), 3.88 (2H, t, J=6.5 Hz), 4.97 (2H, d, J=5.4 Hz), 5.49 (2H, s), 6.32 (1H, dd, J=1.8, 2.9 Hz), 6.40 (1H, dd, J=0.8, 2.9 Hz), 7.31 (1H, dd, J=0.8, 1.8 Hz), 7.75 (1H, s), 8.45 (1H, s).

(5) 4-Butoxy-3-chloromethyl-6,7-dichloro-2-(2-furylmethyl)-1(2H)-isoquinoline (synthesized according to the method similar to that in Example 4 (5))

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.05 (3H, t, J=7.3 Hz), 1.55-1.79 (2H, m), 1.82-1.93 (2H, m), 3.99 (2H, t, J=6.6 Hz), 5.00 (2H, s), 5.46 (2H, s), 6.31 (1H, dd, J=1.9, 3.2 Hz), 6.41 (1H, dd, J=1.1, 3.2 Hz), 7.31 (1H, dd, J=1.1, 1.9 Hz), 7.81 (1H, s), 8.51 (1H, s).

(6) 2-((4-Butoxy-6,7-dichloro-2-(2-furylmethyl)-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 148-149°C.

Elemental analysis for C<sub>27</sub>H<sub>22</sub>N<sub>2</sub>O<sub>5</sub>Cl<sub>2</sub>

Calculated: C, 61.72; H, 4.22; N, 5.33.

Found: C, 61.95; H, 4.51; N, 5.47.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.01 (3H, t, J=7.3 Hz), 1.45-1.63 (2H, m), 1.80-1.94 (2H, m), 4.02 (2H, t, J=6.8 Hz), 5.15 (2H, s), 5.36 (2H, s), 6.05 (1H, dd, J=1.8, 3.2 Hz), 6.17 (1H, dd, J=0.8, 3.2 Hz), 6.89 (1H, dd, J=0.8, 1.8 Hz), 7.69-7.80 (4H, bs), 7.82 (1H, s), 8.49 (1H, s).

(7) Tert-butyl (4-butoxy-6,7-dichloro-2-(2-furylmethyl)-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

Melting point 143-144°C.

Elemental analysis for C<sub>24</sub>H<sub>28</sub>N<sub>2</sub>O<sub>5</sub>Cl<sub>2</sub>

Calculated: C, 58.19; H, 5.70; N, 5.65.

Found: C, 58.31; H, 5.53; N, 5.70.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:1.04 (3H, t, J=7.3 Hz), 1.46 (9H, s),  
1.51-1.67 (2H, m), 1.79-1.93 (2H, m), 3.84 (2H, t, J=6.5  
Hz), 4.66 (2H, d, J=5.8 Hz), 4.91 (1H, bs), 5.37 (2H, s),  
6.30 (1H, dd, J=2.0, 3.4 Hz), 6.44 (1H, d, J=3.4 Hz),  
5 7.32 (1H, d, J=2.0 Hz), 7.75 (1H, s), 8.47 (1H, s).

(8) 3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-(2-furylmethyl)-1(2H)-isoquinolinone hydrochloride  
(synthesized according to the method similar to that in  
Example 1 (7))

10 Melting point 223-224°C.

Elemental analysis for C<sub>19</sub>H<sub>21</sub>N<sub>2</sub>O<sub>3</sub>Cl<sub>2</sub>

Calculated: C, 52.86; H, 4.90; N, 6.49.

Found: C, 52.55; H, 4.97; N, 6.58.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ:0.99 (3H, t, J=7.3 Hz), 1.44-1.63 (2H,  
15 m), 1.77-1.92 (2H, m), 3.94 (2H, t, J=6.4 Hz), 4.26 (2H,  
s), 5.40 (2H, s), 6.42 (1H, dd, J=1.8, 3.2 Hz), 6.45 (1H,  
dd, J=1.0, 3.2 Hz), 7.61 (1H, dd, J=1.0, 1.8 Hz), 7.93  
(1H, s), 8.39 (1H, s), 8.82 (3H, bs).

#### Example 48

20 3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-(2-methoxyethyl)-1(2H)-isoquinolinone hydrochloride

(1) ethyl 6,7-dichloro-4-hydroxy-2-(2-methoxyethyl)-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized  
according to the method similar to that in Example 1

25 (1))

Melting point 110.5-111°C.

Elemental analysis for C<sub>15</sub>H<sub>15</sub>NO<sub>5</sub>Cl<sub>2</sub>

Calculated: C, 50.02; H, 4.20; N, 3.89.

Found: C, 49.86; H, 4.44; N, 3.76.

30 <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:1.46 (3H, t, J=7.1 Hz), 3.30 (3H, s),  
3.62 (2H, d, J=5.8 Hz), 4.49 (2H, q, J=7.1 Hz), 4.61 (2H,  
t, J=5.8 Hz), 8.22 (1H, s), 8.51 (1H, s), 10.95 (1H, s).

(2) Ethyl 4-butoxy-6,7-dichloro-2-(2-methoxyethyl)-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized  
35 according to the method similar to that in Example 1  
(2))



Melting point 102-103°C.

Elemental analysis for  $C_{19}H_{23}NO_5Cl_2$

Calculated: C, 54.82; H, 5.57; N, 3.36.

Found: C, 54.81; H, 5.35; N, 3.36.

- 5  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.01 (3H, t,  $J=7.3$  Hz), 1.44 (3H, t,  $J=7.2$  Hz), 1.50-1.62 (2H, m), 1.72-1.86 (2H, m), 3.31 (3H, s), 3.63 (2H, t,  $J=5.9$  Hz), 3.94 (2H, t,  $J=6.4$  Hz), 4.26 (2H, t,  $J=5.9$  Hz), 4.45 (2H, q,  $J=7.2$  Hz), 7.82 (1H, s), 8.50 (1H, s).

- 10 (3) 4-Butoxy-6,7-dichloro-2-(2-methoxyethyl)-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 142-143°C.

- 15 Elemental analysis for  $C_{17}H_{19}NO_5Cl_2$

Calculated: C, 52.59; H, 4.93; N, 3.61.

Found: C, 52.58; H, 4.94; N, 3.41.

- $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.00 (3H, t,  $J=7.2$  Hz), 1.44-1.63 (2H, m), 1.74-1.89 (2H, m), 3.41 (3H, s), 3.85 (2H, t,  $J=5.3$  Hz), 4.00 (2H, t,  $J=6.4$  Hz), 4.37-4.40 (2H, m), 7.82 (1H, s), 8.48 (1H, s).

- 20 (4) 4-Butoxy-6,7-dichloro-3-hydroxymethyl-2-(2-methoxyethyl)-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4

- 25 (4))

Melting point 122-123°C.

Elemental analysis for  $C_{17}H_{21}NO_4Cl_2$

Calculated: C, 54.56; H, 5.66; N, 3.74.

Found: C, 54.34; H, 5.59; N, 3.57.

- 30  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.04 (3H, t,  $J=7.3$  Hz), 1.50-1.69 (2H, m), 1.80-1.94 (2H, m), 3.34 (3H, s), 3.83 (2H, t,  $J=5.5$  Hz), 3.96 (2H, t,  $J=6.6$  Hz), 4.38 (2H, t,  $J=5.5$  Hz), 4.46 (1H, t,  $J=6.4$  Hz), 4.79 (2H, d,  $J=6.4$  Hz), 7.84 (1H, s), 8.47 (1H, s).

- 35 (5) 4-Butoxy-3-chloromethyl-6,7-dichloro-2-(2-methoxyethyl)-1(2H)-isoquinolinone (synthesized

according to the method similar to that in Example 4  
(5))

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:1.05 (3H, t, J=7.3 Hz), 1.55-1.70 (2H, m), 1.82-1.96 (2H, m), 3.26 (3H, s), 3.69 (2H, t, J=4.8 Hz), 3.98 (2H, t, J=6.4 Hz), 4.43 (2H, t, J=4.8 Hz), 4.99 (2H, s), 7.82 (1H, s), 8.50 (1H, s).

(6) 2-((4-Butoxy-6,7-dichloro-2-(2-methoxyethyl)-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 151-152°C.

Elemental analysis for C<sub>25</sub>H<sub>24</sub>N<sub>2</sub>O<sub>5</sub>Cl<sub>2</sub>

Calculated: C, 59.65; H, 4.81; N, 5.57.

Found: C, 59.52; H, 4.85; N, 5.55.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:1.00 (3H, t, J=7.3 Hz), 1.44-1.62 (2H, m), 1.79-1.93 (2H, m), 2.97 (3H, s), 3.64 (2H, t, J=4.9 Hz), 3.98 (2H, t, J=6.6 Hz), 4.37 (2H, t, J=4.9 Hz), 5.10 (2H, s), 7.68-7.87 (5H, m), 8.47 (1H, s).

(7) Tert-butyl {4-butoxy-6,7-dichloro-2-(2-methoxyethyl)-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

Melting point 137-138°C.

Elemental analysis for C<sub>22</sub>H<sub>30</sub>N<sub>2</sub>O<sub>5</sub>Cl<sub>2</sub>

Calculated: C, 55.82; H, 6.39; N, 5.92.

Found: C, 55.99; H, 6.33; N, 5.76.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:1.03 (3H, t, J=7.3 Hz), 1.46 (9H, s), 1.51-1.64 (2H, m), 1.81-1.95 (2H, m), 3.33 (3H, s), 3.80 (2H, t, J=4.5 Hz), 3.85 (2H, t, J=6.6 Hz), 4.30 (2H, t, J=4.5 Hz), 4.54 (2H, d, J=5.2 Hz), 6.15 (1H, bs), 7.80 (1H, s), 8.46 (1H, s).

(8) 3-(Aminomethyl)-4-butoxy-6,7-dichloro-2-(2-methoxyethyl)-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 241.5-242°C.

Elemental analysis for  $C_{17}H_{23}N_2O_3Cl_3$

Calculated: C, 49.83; H, 5.66; N, 6.84.

Found: C, 49.80; H, 5.91; N, 6.81.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.99 (3H, t,  $J=7.3$  Hz), 1.45-1.63 (2H, m), 1.77-1.91 (2H, m), 3.24 (3H, s), 3.61 (2H, d,  $J=4.9$  Hz), 3.93 (2H, t,  $J=6.6$  Hz), 4.23-4.32 (4H, m), 7.91 (1H, s), 8.38 (1H, s), 8.68 (3H, bs).

#### Example 49

3-(Aminomethyl)-4-(2-methoxyethoxy)-2-neopentyl-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 4-(2-methoxyethoxy)-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.94 (9H, s), 1.43 (3H, t,  $J=7.2$  Hz), 3.48 (3H, s), 3.71-3.75 (2H, m), 4.07-4.17 (2H, m), 4.43 (2H, q,  $J=7.2$  Hz), 7.53-7.61 (1H, m), 7.69-7.77 (1H, m), 7.93-7.97 (1H, m), 8.42-8.47 (1H, m).

(2) 4-(2-Methoxyethoxy)-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 148-149°C.

Elemental analysis for  $C_{18}H_{23}NO_5$

Calculated: C, 64.85; H, 6.95; N, 4.20.

Found: C, 64.79; H, 6.96; N, 4.09.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.94 (9H, s), 3.49 (3H, s), 3.76-3.81 (2H, m), 4.27-4.32 (4H, m), 7.56-7.64 (1H, m), 7.70-7.78 (1H, m), 7.89 (1H, dd,  $J=0.8, 8.0$  Hz), 8.44 (1H, dd,  $J=1.0, 8.0$  Hz), 9.79 (1H, bs).

(3) 3-Hydroxymethyl-4-(2-methoxyethoxy)-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

Melting point 145-145.5°C.

Elemental analysis for  $C_{18}H_{25}NO_4$

Calculated: C, 67.69; H, 7.89; N, 4.39.

Found: C, 67.54; H, 8.06; N, 4.28.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.98 (9H, s), 3.45 (3H, s), 3.58 (1H, t,

J=6.8 Hz), 3.75-3.79 (2H, m), 4.14-4.18 (2H, m), 4.23 (2H, bs), 4.90 (2H, bs), 7.44-7.52 (1H, m), 7.63-7.76 (2H, m), 8.40 (1H, dd, J=0.8, 8.0 Hz).

(4) 3-Chloromethyl-4-(2-methoxyethoxy)-2-neopentyl-  
5 1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.98 (9H, s), 3.52 (3H, s), 3.76-3.82 (2H, m), 4.11-4.18 (2H, m), 4.21 (2H, bs), 4.96 (2H, bs), 7.50-7.58 (1H, m), 7.67-7.76 (1H, m), 7.87 (1H, dd, J=0.8, 8.0 Hz), 8.44 (1H, dd, J=0.8, 8.0 Hz).

(5) 2-((4-(2-Methoxyethoxy)-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-  
dione (synthesized according to the method similar to that in Example 4 (6))

15 Melting point 145-146°C.

Elemental analysis for C<sub>26</sub>H<sub>28</sub>N<sub>2</sub>O<sub>5</sub>

Calculated: C, 68.93; H, 6.34; N, 6.18.

Found: C, 69.07; H, 6.06; N, 6.53.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:1.00 (9H, s), 3.47 (3H, s), 3.78-3.82 (2H, m), 4.24-4.29 (2H, m), 4.31 (2H, bs), 5.12 (2H, bs), 7.45-7.54 (1H, m), 7.65-7.92 (6H, m), 8.41 (1H, dd, J=0.7, 8.1 Hz).

(6) Tert-butyl ((4-(2-methoxyethoxy)-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl)carbamate (synthesized  
25 according to the method similar to that in Example 1 (6))

Melting point 143-144°C.

Elemental analysis for C<sub>23</sub>H<sub>34</sub>N<sub>2</sub>O<sub>5</sub>

Calculated: C, 66.00; H, 8.19; N, 6.69.

30 Found: C, 65.73; H, 8.14; N, 6.78.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.99 (9H, s), 1.44 (9H, s), 3.48 (3H, s), 3.74-3.79 (2H, m), 4.07-4.12 (2H, m), 4.19 (2H, bs), 4.61 (2H, d, J=6.0 Hz), 5.17 (1H, bs), 7.46-7.54 (1H, m), 7.65-7.73 (1H, m), 7.79 (1H, d, J=8.2 Hz), 8.42 (1H, dd, J=0.7, 8.2 Hz).

(7) 3-(Aminomethyl)-4-(2-methoxyethoxy)-2-neopentyl-

1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 205-206°C.

5 Elemental analysis for  $C_{18}H_{27}N_2O_3Cl \cdot 1/4H_2O$

Calculated: C, 60.16; H, 7.71; N, 7.80.

Found: C, 59.84; H, 7.52; N, 7.82.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.91 (9H, s), 1.10 (6H, d, J=6.6 Hz),  
2.14-2.27 (1H, m), 3.73 (2H, d, J=6.6 Hz), 4.11 (2H, bs),  
10 4.24 (2H, s), 7.89 (1H, s), 8.38 (1H, s), 8.63 (3H, bs).

Example 50

3-(Aminomethyl)-4-butoxy-7-methyl-2-neopentyl-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 4-hydroxy-7-methyl-2-neopentyl-1-oxo-1,2-  
15 dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (1))

Melting point 90-91°C.

Elemental analysis for  $C_{18}H_{23}NO_4$

Calculated: C, 68.12; H, 7.30; N, 4.41.

20 Found: C, 67.98; H, 7.10; N, 4.22.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.84 (9H, s), 1.46 (3H, t, J=7.1 Hz),  
2.54 (3H, s), 4.42 (2H, bs), 4.49 (2H, q, J=7.1 Hz),  
7.57 (1H, dd, J=1.9, 8.0 Hz), 8.04 (1H, d, J=8.0 Hz),  
8.26 (1H, d, J=1.9 Hz), 10.90 (1H, s).

25 (2) Ethyl 4-butoxy-7-methyl-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.93 (9H, s), 1.00 (3H, t, J=7.3 Hz),  
1.44 (3H, t, J=7.0 Hz), 1.47-1.62 (2H, m), 1.73-1.87 (2H,  
30 m), 2.51 (3H, s), 3.95 (2H, t, J=6.6 Hz), 4.11 (2H, bs),  
4.42 (2H, q, J=7.0 Hz), 7.54 (1H, dd, J=1.7, 8.0 Hz),  
7.68 (1H, d, J=8.0 Hz), 8.26 (1H, d, J=1.7 Hz).

(3) 4-Butoxy-7-methyl-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to  
35 the method similar to that in Example 4 (3))

Melting point 160.5-161°C.

Elemental analysis for  $C_{20}H_{27}NO_4$

Calculated: C, 69.54; H, 7.88; N, 4.05.

Found: C, 69.45; H, 8.10; N, 3.98.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.91 (9H, s), 0.99 (3H, t,  $J=7.1$  Hz),  
5 1.44-1.63 (2H, m), 1.76-1.90 (2H, m), 2.50 (3H, s), 4.00  
(2H, t,  $J=6.6$  Hz), 4.26 (2H, bs), 5.92 (1H, bs), 7.45-  
7.56 (2H, m), 8.13 (1H, s).

(4) 4-Butoxy-3-hydroxymethyl-7-methyl-2-neopentyl-1(2H)-  
isoquinoline (synthesized according to the method  
10 similar to that in Example 4 (4)).

Melting point 109-110°C.

Elemental analysis for  $C_{20}H_{29}NO_3$

Calculated: C, 72.47; H, 8.82; N, 4.23.

Found: C, 72.18; H, 8.75; N, 4.26.

15  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.96 (9H, s), 1.03 (3H, t,  $J=7.4$  Hz),  
1.49-1.68 (2H, m), 1.79-1.93 (2H, m), 2.45 (3H, s), 2.61  
(1H, bs), 3.90 (2H, t,  $J=6.6$  Hz), 4.22 (2H, bs), 4.87  
(2H, bs), 7.43 (1H, dd,  $J=1.8, 8.0$  Hz), 7.56 (1H, d,  
 $J=8.0$  Hz), 8.09 (1H, d,  $J=1.8$  Hz).

20 (5) 4-Butoxy-3-chloromethyl-7-methyl-2-neopentyl-1(2H)-  
isoquinoline (synthesized according to the method  
similar to that in Example 4 (5))

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.98 (9H, s), 1.04 (3H, t,  $J=7.3$  Hz),  
1.51-1.69 (2H, m), 1.81-1.95 (2H, m), 2.50 (3H, s), 3.95  
25 (2H, t,  $J=6.4$  Hz), 4.18 (2H, bs), 4.90 (2H, bs), 7.52  
(1H, dd,  $J=1.8, 8.1$  Hz), 7.65 (1H, d,  $J=8.1$  Hz), 8.24  
(1H, d,  $J=1.8$  Hz).

(6) 2-((4-Butoxy-7-methyl-2-neopentyl-1-oxo-1,2-dihydro-  
3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-dione  
30 (synthesized according to the method similar to that in  
Example 4 (6))

Melting point 174-175°C.

Elemental analysis for  $C_{28}H_{32}N_2O_4 \cdot 1/4H_2O$

Calculated: C, 72.31; H, 7.04; N, 6.02.

35 Found: C, 72.57; H, 7.35; N, 6.04.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.00 (9H, s), 1.01 (3H, t,  $J=7.3$  Hz),

1.44-1.59 (2H, m), 1.81-1.95 (2H, m), 2.48 (3H, s), 4.02 (2H, t, J=6.8 Hz), 4.10 (2H, bs), 5.08 (2H, s), 7.50 (1H, dd, J=1.7, 8.3 Hz), 7.63-7.82 (5H, m), 8.22 (1H, d, J=1.7 Hz).

- 5 (7) Tert-butyl (4-butoxy-7-methyl-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

Melting point 153-154°C.

- 10 Elemental analysis for  $C_{25}H_{38}N_2O_4$

Calculated: C, 69.74; H, 8.90; N, 6.51.

Found: C, 69.65; H, 9.13; N, 6.56.

- $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (9H, s), 1.03 (3H, t, J=7.2 Hz), 1.45 (9H, s), 1.52-1.63 (2H, m), 1.79-1.93 (2H, m), 2.49 (3H, s), 3.86 (2H, t, J=6.5 Hz), 4.18 (2H, bs), 4.56 (2H, t, J=5.4 Hz), 4.68 (1H, bs), 7.50 (1H, dd, J=1.8, 8.0 Hz), 7.60 (1H, d, J=8.0 Hz), 8.21 (1H, d, J=1.8 Hz).

- 15 (8) 3-(Aminomethyl)-4-butoxy-7-methyl-2-neopentyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 231-233°C.

Elemental analysis for  $C_{20}H_{31}N_2O_2Cl$

Calculated: C, 65.47; H, 8.52; N, 7.63.

Found: C, 65.44; H, 8.53; N, 7.86.

- 25  $^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.99 (9H, s), 0.99 (3H, t, J=7.2 Hz), 1.45-1.64 (2H, m), 1.77-1.91 (2H, m), 2.47 (3H, s), 3.92 (2H, t, J=6.6 Hz), 4.10 (2H, bs), 4.23 (2H, d, J=5.2 Hz), 7.63-7.72 (2H, m), 8.09 (1H, s), 8.56 (3H, bs).

#### Example 51

- 30 3-(Aminomethyl)-4-butoxy-6-methyl-2-neopentyl-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 4-hydroxy-6-methyl-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (1))

- 35  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.84 (9H, s), 1.46 (3H, t, J=7.2 Hz), 2.54 (3H, s), 4.42 (2H, bs), 4.47 (2H, q, J=7.2 Hz),

7.51 (1H, dd, J=1.9, 8.0 Hz), 7.93 (1H, d, J=1.9 Hz),  
8.33 (1H, d, J=8.0 Hz), 10.86 (1H, s).

(2) Ethyl 4-butoxy-6-methyl-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2)).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.94 (9H, s), 1.00 (3H, t, J=7.2 Hz),  
1.44 (3H, t, J=7.2 Hz), 1.47-1.60 (2H, m), 1.74-1.91 (2H, m),  
2.52 (3H, s), 3.96 (2H, t, J=6.4 Hz), 4.07 (2H, bs),  
4.43 (2H, q, J=7.2 Hz), 7.38 (1H, dd, J=1.0, 8.0 Hz),  
7.68 (1H, d, J=1.0 Hz), 8.26 (1H, d, J=8.0 Hz).

(3) 4-Butoxy-6-methyl-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3)).

Melting point 153-154°C.

Elemental analysis for C<sub>20</sub>H<sub>27</sub>NO<sub>4</sub>

Calculated: C, 69.54; H, 7.88; N, 4.05.

Found: C, 69.59; H, 8.16; N, 4.06.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.91 (9H, s), 1.01 (3H, t, J=7.1 Hz),  
1.48-1.65 (2H, m), 1.77-1.88 (2H, m), 2.52 (3H, s), 4.02  
(2H, t, J=6.4 Hz), 4.22 (2H, bs), 6.42 (1H, bs), 7.38  
(1H, dd, J=1.3, 8.2 Hz), 7.45 (1H, d, J=1.3 Hz), 8.25  
(1H, d, J=8.2 Hz).

(4) 4-Butoxy-3-hydroxymethyl-6-methyl-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the method

similar to that in Example 4 (4)).

Melting point 133-134°C.

Elemental analysis for C<sub>20</sub>H<sub>29</sub>NO<sub>3</sub>

Calculated: C, 72.47; H, 8.82; N, 4.23.

Found: C, 72.43; H, 8.80; N, 4.24.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.97 (9H, s), 1.04 (3H, t, J=7.2 Hz),  
1.51-1.69 (2H, m), 1.80-1.94 (2H, m), 2.38 (1H, bs),  
2.49 (3H, s), 3.90 (2H, t, J=6.6 Hz), 4.20 (2H, bs),  
4.86 (2H, bs), 7.27 (1H, dd, J=1.6, 8.0 Hz), 7.45 (1H, d,  
J=1.6 Hz), 8.22 (1H, d, J=8.0 Hz).

(5) 4-Butoxy-3-chloromethyl-6-methyl-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the method



similar to that in Example 4 (5))

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.98 (9H, s), 1.05 (3H, t, J=7.1 Hz),  
1.56-1.71 (2H, m), 1.82-1.92 (2H, m), 2.52 (3H, s), 3.95  
(2H, t, J=6.5 Hz), 4.14 (2H, bs), 4.88 (2H, bs), 7.35  
5 (1H, dd, J=1.8, 8.0 Hz), 7.51 (1H, d, J=1.8 Hz), 8.32  
(1H, d, J=8.0 Hz).

(6) 2-((4-Butoxy-6-methyl-2-neopentyl-1-oxo-1,2-dihydro-  
3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-dione  
(synthesized according to the method similar to that in  
10 Example 4 (6))

Melting point 170-172°C.

Elemental analysis for C<sub>28</sub>H<sub>32</sub>N<sub>2</sub>O<sub>4</sub>

Calculated: C, 73.02; H, 7.00; N, 6.08.

Found: C, 72.72; H, 7.05; N, 6.25.

15 <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:1.00 (9H, s), 1.01 (3H, t, J=7.2 Hz),  
1.50-1.65 (2H, m), 1.82-1.93 (2H, m), 2.50 (3H, s), 4.03  
(2H, t, J=6.8 Hz), 4.06 (2H, bs), 5.08 (2H, s), 7.31 (1H,  
dd, J=1.4, 8.2 Hz), 7.53 (1H, d, J=1.4 Hz), 7.68-7.82  
(4H, m), 8.29 (1H, d, J=8.2 Hz).

20 (7) Tert-butyl (4-butoxy-6-methyl-2-neopentyl-1-oxo-1,2-  
dihydro-3-isoquinolinyl)methylcarbamate (synthesized  
according to the method similar to that in Example 1  
(6))

Melting point 127-129°C.

25 Elemental analysis for C<sub>25</sub>H<sub>38</sub>N<sub>2</sub>O<sub>4</sub>

Calculated: C, 69.74; H, 8.90; N, 6.51.

Found: C, 69.80; H, 8.75; N, 6.46.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.99 (9H, s), 1.00 (3H, t, J=7.6 Hz),  
1.45 (9H, s), 1.53-1.68 (2H, m), 1.75-1.94 (2H, m), 2.51  
30 (3H, s), 3.87 (2H, t, J=6.6 Hz), 4.14 (2H, bs), 4.56 (2H,  
d, J=5.2 Hz), 4.65 (1H, bs), 7.32 (1H, dd, J=1.4, 8.4  
Hz), 7.47 (1H, d, J=1.4 Hz), 8.30 (1H, d, J=8.4 Hz).

(8) 3-(Aminomethyl)-4-butoxy-6-methyl-2-neopentyl-1(2H)-  
isoquinolinone hydrochloride (synthesized according to  
35 the method similar to that in Example 1 (7))

Melting point 201-203°C.

Elemental analysis for  $C_{20}H_{31}N_2O_2Cl$

Calculated: C, 65.47; H, 8.52; N, 7.63.

Found: C, 65.50; H, 8.59; N, 7.56.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.90 (9H, s), 1.00 (3H, t,  $J=7.3$  Hz),  
5 1.50-1.65 (2H, m), 1.78-1.91 (2H, m), 2.50 (3H, s), 3.93  
(2H, t,  $J=6.2$  Hz), 4.09 (2H, bs), 4.23 (2H, bs), 7.31  
(1H, d,  $J=8.0$  Hz), 7.55 (1H, s), 8.16 (1H, d,  $J=8.0$  Hz),  
8.58 (3H, bs).

**Example 52**

10 3-(Aminomethyl)-4-butoxy-2-neopentyl-7-trifluoromethyl-  
1(2H)-isoquinolinone hydrochloride

(1) Ethyl 4-hydroxy-2-neopentyl-1-oxo-7-trifluoromethyl-  
1,2-dihydro-3-isoquinolinecarboxylate (synthesized  
according to the method similar to that in Example 1

15: (1))

Melting point 133.5-134°C.

Elemental analysis for  $C_{18}H_{20}NO_4F_3$

Calculated: C, 58.22; H, 5.43; N, 3.77.

Found: C, 58.24; H, 5.48; N, 3.76.

20  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.86 (9H, s), 1.48 (3H, t,  $J=7.2$  Hz),  
4.45 (2H, bs), 4.50 (2H, q,  $J=7.2$  Hz), 7.96 (1H, dd,  
 $J=1.8, 8.4$  Hz), 8.27 (1H, d,  $J=8.4$  Hz), 8.75 (1H, d,  
 $J=1.8$  Hz), 10.71 (1H, s).

(2) Ethyl 4-butoxy-2-neopentyl-1-oxo-7-trifluoromethyl-  
25 1,2-dihydro-3-isoquinolinecarboxylate (synthesized  
according to the method similar to that in Example 1  
(2))

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.95 (9H, s), 1.01 (3H, t,  $J=7.3$  Hz),  
1.45 (3H, t,  $J=7.1$  Hz), 1.52-1.63 (2H, m), 1.74-1.88 (2H,  
30 m), 3.96 (2H, t,  $J=6.6$  Hz), 4.09 (2H, bs), 4.45 (2H, q,  
 $J=7.1$  Hz), 7.90-7.94 (2H, m), 8.73-8.75 (1H, m).

(3) 4-Butoxy-2-neopentyl-1-oxo-7-trifluoromethyl-1,2-  
dihydro-3-isoquinolinecarboxylic acid (synthesized  
according to the method similar to that in Example 4

35: (3))

Melting point 169-170°C.

Elemental analysis for  $C_{20}H_{24}NO_4F_3$

Calculated: C, 60.14; H, 6.06; N, 3.51.

Found: C, 60.17; H, 5.94; N, 3.45.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.95 (9H, s), 1.00 (3H, t,  $J=7.4$  Hz),  
5 1.45-1.64 (2H, m), 1.78-1.92 (2H, m), 4.03 (2H, t,  $J=6.6$   
Hz), 4.26 (2H, bs), 5.02 (1H, bs), 7.84-7.95 (2H, m),  
8.70 (1H, s).

(4) 4-Butoxy-3-hydroxymethyl-2-neopentyl-7-  
trifluoromethyl-1(2H)-isoquinolinone (synthesized  
10 according to the method similar to that in Example 4  
(4))

Melting point 98-99°C.

Elemental analysis for  $C_{20}H_{26}NO_3F_3 \cdot 1/4H_2O$

Calculated: C, 61.31; H, 6.85; N, 3.59.

15 Found: C, 61.54; H, 6.83; N, 3.79.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.95 (9H, s), 1.05 (3H, t,  $J=7.3$  Hz),  
1.51-1.70 (2H, m), 1.81-1.95 (2H, m), 3.02 (1H, bs),  
3.91 (2H, t,  $J=6.4$  Hz), 4.25 (2H, bs), 4.89 (2H, bs),  
7.70-7.75 (2H, m), 8.45 (1H, s).

20 (5) 4-Butoxy-3-chloromethyl-2-neopentyl-7-  
trifluoromethyl-1(2H)-isoquinolinone (synthesized  
according to the method similar to that in Example 4  
(5))

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (9H, s), 1.04 (3H, t,  $J=7.4$  Hz),  
25 1.52-1.76 (2H, m), 1.82-1.96 (2H, m), 3.95 (2H, t,  $J=6.4$   
Hz), 4.22 (2H, bs), 4.89 (2H, bs), 7.83-7.93 (2H, m),  
8.72-8.74 (1H, m).

(6) 2-((4-Butoxy-2-neopentyl-1-oxo-7-trifluoromethyl-  
1,2-dihydro-3-isoquinolinyl)methyl)-1H-isoindole-  
30 1,3(2H)-dione (synthesized according to the method  
similar to that in Example 4 (6))

Melting point 132-133°C.

Elemental analysis for  $C_{28}H_{29}N_2O_4F_3$

Calculated: C, 65.36; H, 5.68; N, 5.44.

35 Found: C, 65.34; H, 5.38; N, 5.49.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.01 (3H, t,  $J=7.3$  Hz), 1.02 (9H, s),

1.46-1.62 (2H, m), 1.82-1.93 (2H, m), 4.02 (2H, t, J=6.8 Hz), 4.05 (2H, bs), 5.09 (2H, s), 7.70-7.86 (6H, m), 8.70 (1H, s).

- (7) Tert-butyl (4-butoxy-2-neopentyl-1-oxo-7-trifluoromethyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

Elemental analysis for  $C_{25}H_{35}N_2O_4F_3$

Calculated: C, 61.97; H, 7.28; N, 5.78.

- 10 Found: C, 61.86; H, 7.38; N, 5.73.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.00 (9H, s), 1.04 (3H, t, J=7.4 Hz), 1.46 (9H, s), 1.53-1.68 (2H, m), 1.81-1.95 (2H, m), 3.87 (2H, t, J=6.6 Hz), 4.14 (2H, bs), 4.59 (2H, d, J=5.0 Hz), 4.82 (1H, bs), 7.77-7.88 (2H, m), 8.66 (1H, d, J=0.6 Hz).

- 15 (8) 3-(Aminomethyl)-4-butoxy-2-neopentyl-7-trifluoromethyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 224-225°C.

- 20 Elemental analysis for  $C_{20}H_{28}N_2O_2ClF_3$

Calculated: C, 57.07; H, 6.71; N, 6.66.

Found: C, 56.77; H, 6.69; N, 6.73.

- $^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.92 (9H, s), 1.00 (3H, t, J=7.3 Hz), 1.50-1.61 (2H, m), 1.80-1.92 (2H, m), 3.96 (2H, t, J=6.4 Hz), 4.15 (2H, bs), 4.29 (2H, bs), 8.00 (1H, d, J=8.4 Hz), 8.17 (1H, dd, J=1.8, 8.4 Hz), 8.52 (1H, d, J=1.8 Hz), 8.66 (3H, bs).

#### Example 53

- 30 3-(Aminomethyl)-4-butoxy-2-neopentyl-6-trifluoromethyl-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 4-hydroxy-2-neopentyl-1-oxo-6-trifluoromethyl-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (1))

- 35  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.86 (9H, s), 1.49 (3H, t, J=7.2 Hz), 4.46 (2H, bs), 4.51 (2H, q, J=7.2 Hz), 7.89 (1H, dd,

J=2.0, 8.4 Hz), 8.43 (1H, d, J=2.0 Hz), 8.57 (1H, d, J=8.4 Hz), 10.79 (1H, s).

(2) Ethyl 4-butoxy-2-neopentyl-1-oxo-6-trifluoromethyl-1,2-dihydro-3-isoquinolinecarboxylate (synthesized

5 according to the method similar to that in Example 1 (2))

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.95 (9H, s), 1.02 (3H, t, J=7.4 Hz), 1.45 (3H, t, J=7.1 Hz), 1.49-1.66 (2H, m), 1.76-1.90 (2H, m), 3.98 (2H, t, J=6.4 Hz), 4.11 (2H, bs), 4.46 (2H, q, J=7.1 Hz), 7.78 (1H, dd, J=1.6, 8.4 Hz), 8.05 (1H, d, J=1.6 Hz), 8.57 (1H, d, J=8.4 Hz).

(3) 4-Butoxy-2-neopentyl-1-oxo-6-trifluoromethyl-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4

15 (3))

Melting point 164-166°C.

Elemental analysis for C<sub>20</sub>H<sub>24</sub>NO<sub>4</sub>F<sub>3</sub>

Calculated: C, 60.14; H, 6.06; N, 3.51.

Found: C, 60.15; H, 5.86; N, 3.43.

20 <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.95 (9H, s), 1.01 (3H, t, J=7.2 Hz), 1.48-1.66 (2H, m), 1.78-1.92 (2H, m), 4.04 (2H, t, J=6.4 Hz), 4.28 (2H, bs), 5.01 (1H, bs), 7.79 (1H, dd, J=1.4, 8.6 Hz), 8.00 (1H, d, J=1.4 Hz), 8.54 (1H, d, J=8.6 Hz).

(4) 4-Butoxy-3-hydroxymethyl-2-neopentyl-6-

25 trifluoromethyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4

(4))

Melting point 107-108°C.

Elemental analysis for C<sub>20</sub>H<sub>26</sub>NO<sub>3</sub>F<sub>3</sub>

30 Calculated: C, 62.33; H, 6.80; N, 3.63.

Found: C, 62.31; H, 6.74; N, 3.74.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.97 (9H, s), 1.08 (3H, t, J=6.9 Hz), 1.52-1.71 (2H, m), 1.81-1.95 (2H, m), 2.48 (1H, bs), 3.91 (2H, t, J=6.4 Hz), 4.23 (2H, bs), 4.89 (2H, bs), 7.63 (1H, d, J=8.5 Hz), 7.94 (1H, s), 8.42 (1H, d, J=8.5 Hz).

(5) 4-Butoxy-3-chloromethyl-2-neopentyl-6-trifluoromethyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.99 (9H, s), 1.05 (3H, t, J=7.3 Hz), 1.54-1.72 (2H, m), 1.83-1.97 (2H, m), 3.96 (2H, t, J=6.4 Hz), 4.22 (2H, bs), 4.89 (2H, bs), 7.74 (1H, dd, J=1.6, 8.6 Hz), 8.02 (1H, d, J=1.6 Hz), 8.55 (1H, d, J=8.6 Hz).

(6) 2-((4-Butoxy-2-neopentyl-1-oxo-6-trifluoromethyl-1,2-dihydro-3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Melting point 123-124°C.

Elemental analysis for C<sub>28</sub>H<sub>29</sub>N<sub>2</sub>O<sub>4</sub>F<sub>3</sub>

Calculated: C, 65.36; H, 5.68; N, 5.44.

Found: C, 65.44; H, 5.77; N, 5.48.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:1.01 (9H, s), 1.02 (3H, t, J=7.3 Hz), 1.48-1.67 (2H, m), 1.83-1.97 (2H, m), 4.04 (2H, t, J=6.6 Hz), 4.07 (2H, bs), 5.09 (2H, s), 7.67-7.84 (5H, m), 8.03 (1H, s), 8.52 (1H, d, J=8.4 Hz).

(7) Tert-butyl (4-butoxy-2-neopentyl-1-oxo-6-trifluoromethyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

Melting point 153-154°C.

Elemental analysis for C<sub>25</sub>H<sub>35</sub>N<sub>2</sub>O<sub>4</sub>F<sub>3</sub>

Calculated: C, 61.97; H, 7.28; N, 5.78.

Found: C, 61.71; H, 7.09; N, 5.75.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:1.00 (9H, s), 1.04 (3H, t, J=7.4 Hz), 1.45 (9H, s), 1.51-1.70 (2H, m), 1.81-1.95 (2H, m), 3.88 (2H, t, J=6.4 Hz), 4.14 (2H, bs), 4.59 (2H, d, J=5.8 Hz), 4.73 (1H, bs), 7.69 (1H, dd, J=1.6, 8.2 Hz), 7.96 (1H, d, J=1.6 Hz), 8.52 (1H, d, J=8.2 Hz).

(8) 3-(Aminomethyl)-4-butoxy-2-neopentyl-6-trifluoromethyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in

## Example 1 (7))

Melting point 206-208°C.

Elemental analysis for  $C_{20}H_{28}N_2O_2ClF_3 \cdot 1/2H_2O$ 

Calculated: C, 55.88; H, 6.80; N, 6.52.

5 Found: C, 55.71; H, 6.58; N, 6.19.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.92 (9H, s), 1.00 (3H, t, J=7.4 Hz), 1.52-1.64 (2H, m), 1.78-1.92 (2H, m), 3.97 (2H, t, J=6.5 Hz), 4.14 (2H, bs), 4.29 (2H, bs), 7.94 (1H, d, J=8.6 Hz), 8.00 (1H, s), 8.49 (1H, d, J=8.6 Hz), 8.61 (3H, bs).

## 10 Example 54

Methyl 3-{2-[3-(aminomethyl)-4-butoxy-6,7-dichloro-1-oxo-2(1H)-isoquinolinyl]ethylcarbamate hydrochloride

(1) A solution of 3-[4-butoxy-6,7-dichloro-3-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-1-oxo-2(1H)-

15 isoquinolinyl]propionic acid (0.78 g, 1.5 mmol), diphenylphosphoryl azide (0.39 ml, 1.8 mmol) and triethylamine (0.25 ml, 1.8 mmol) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 2 h. The reaction mixture was poured  
20 into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in toluene (20 ml) and the mixture was refluxed with stirring. To the  
25 obtained mixture was added methanol (1 ml) and the mixture was refluxed with stirring for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated  
30 under reduced pressure. The residue was recrystallized from tetrahydrofuran - diisopropyl ether to give methyl 2-[4-butoxy-6,7-dichloro-3-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-1-oxo-2(1H)-isoquinolinyl]ethylcarbamate (0.30 g, 36.6%) as crystals.

35 Melting point 241-243°C.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (3H, t, J=7.3 Hz), 1.43-1.58 (2H,

m), 1.72-1.91 (2H, m), 3.51 (2H, q, J=6.6 Hz), 3.61 (3H, s), 3.91 (2H, t, J=6.8 Hz), 4.45 (2H, t, J=6.6 Hz), 5.07 (2H, s), 5.47 (1H, bs), 7.71-7.88 (5H, m), 8.47 (1H, s).

(2) Methyl 2-{4-butoxy-3-((tert-butoxycarbonyl)amino)methyl}-6,7-dichloro-1-oxo-2(1H)-isoquinolinyl}ethylcarbamate (synthesized according to the method similar to that in Example 1 (6)).

Melting point 185.5-186°C.

Elemental analysis for  $C_{23}H_{31}N_3O_6Cl_2$

10 Calculated: C, 53.49; H, 6.05; N, 8.14.

Found: C, 53.64; H, 6.11; N, 8.30.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.04 (3H, t, J=7.3 Hz), 1.46 (9H, s), 1.52-1.67 (2H, m), 1.80-1.94 (2H, m), 3.54 (2H, t, J=6.2 Hz), 3.59 (3H, s), 3.85 (2H, t, J=6.5 Hz), 4.29 (2H, t, J=6.2 Hz), 4.52 (2H, d, J=5.8 Hz), 5.34 (1H, s), 5.51 (1H, bs), 7.78 (1H, s), 8.46 (1H, s).

(3) Methyl 3-{2-{3-(aminomethyl)-4-butoxy-6,7-dichloro-1-oxo-2(1H)-isoquinolinyl}ethylcarbamate hydrochloride (synthesized according to the method similar to that in Example 1 (7)).

Melting point 230-231°C.

Elemental analysis for  $C_{18}H_{24}N_3O_4Cl_3$

Calculated: C, 47.75; H, 5.34; N, 9.28.

Found: C, 47.47; H, 5.47; N, 9.10.

25  $^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.99 (3H, t, J=7.3 Hz), 1.45-1.63 (2H, m), 1.76-1.91 (2H, m), 3.29 (2H, q, J=6.4 Hz), 3.47 (3H, s), 3.91 (2H, t, J=6.4 Hz), 4.12 (2H, t, J=6.4 Hz), 4.23 (2H, d, J=4.4 Hz), 7.44 (1H, bs), 7.93 (1H, s), 8.39 (1H, s), 8.72 (3H, bs).

30 Example 55

N-{2-{3-(Aminomethyl)-4-butoxy-6,7-dichloro-1-oxo-2(1H)-isoquinolinyl}ethyl}-1-pyrrolidinecarboxamide hydrochloride

(1) N-{2-{4-Butoxy-6,7-dichloro-3-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-1-oxo-2(1H)-isoquinolinyl}ethyl}-1-pyrrolidinecarboxamide



(synthesized according to the method similar to that in Example 4 (6))

Melting point 197-198°C.

Elemental analysis for  $C_{29}H_{30}N_4O_5Cl_2 \cdot 1/2H_2O$

5 Calculated: C, 58.59; H, 5.26; N, 9.42.

Found: C, 58.58; H, 5.54; N, 9.32.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.98 (3H, t, J=7.3 Hz), 1.38-1.57 (2H, m), 1.76-1.89 (6H, m), 3.23-3.30 (4H, m), 3.56 (2H, q, J=6.6 Hz), 3.89 (2H, t, J=6.8 Hz), 4.53 (2H, t, J=6.6 Hz), 5.08 (1H, bs), 5.12 (2H, s), 7.70-7.85 (5H, m), 8.47 (1H, s).

(2) Tert-butyl {4-butoxy-6,7-dichloro-1-oxo-2-{2-(1-pyrrolidinylcarbonyl)amino}ethyl}-1,2-dihydro-3-isoquinolinyl}methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

Melting point 161-162°C.

Elemental analysis for  $C_{26}H_{36}N_4O_5Cl_2$

Calculated: C, 56.22; H, 6.53; N, 10.09.

Found: C, 56.61; H, 6.24; N, 9.99.

20  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.03 (3H, t, J=7.3 Hz), 1.45 (9H, s), 1.52-1.66 (2H, m), 1.80-1.91 (8H, m), 3.17-3.24 (4H, m), 3.61 (2H, q, J=6.3 Hz), 3.88 (2H, t, J=6.6 Hz), 4.32 (2H, t, J=6.3 Hz), 4.53 (2H, d, J=6.0 Hz), 5.09 (1H, bs), 6.07 (1H, bs), 7.81 (1H, s), 8.44 (1H, s).

25 (3) N-{2-{3-(Aminomethyl)-4-butoxy-6,7-dichloro-1-oxo-2(1H)-isoquinolinyl}ethyl}-1-pyrrolidinecarboxylic acid hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 190-192°C.

30 Elemental analysis for  $C_{21}H_{29}N_4O_3Cl_3 \cdot 3/2H_2O$

Calculated: C, 48.61; H, 6.17; N, 10.80.

Found: C, 48.85; H, 6.06; N, 10.81.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.99 (3H, t, J=7.3 Hz), 1.48-1.63 (2H, m), 1.79-1.91 (6H, m), 3.16-3.28 (6H, m), 3.92 (2H, t, J=6.4 Hz), 4.09 (2H, t, J=6.8 Hz), 4.31 (2H, bs), 6.80 (1H, bs), 7.92 (1H, s), 8.38 (1H, s), 8.95 (3H, bs).

**Example 56**

3-(Aminomethyl)-4-butoxy-2-neopentylbenzo{g}isoquinolin-1(2H)-one hydrochloride

- (1) Ethyl 4-hydroxy-2-neopentyl-1-oxo-1,2-dihydrobenzo-  
5 {g}isoquinoline-3-carboxylate (synthesized according to the method similar to that in Example 1 (1))

Melting point 140-141.5°C.

Elemental analysis for  $C_{21}H_{23}NO_4$

Calculated: C, 71.37; H, 6.56; N, 3.96.

- 10 Found: C, 71.08; H, 6.36; N, 3.72.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.87 (9H, s), 1.48 (3H, t,  $J=7.2$  Hz),  
4.50 (2H, q,  $J=7.2$  Hz), 4.55 (2H, bs), 7.59-7.69 (2H, m),  
8.05-8.12 (2H, m), 8.67 (1H, s), 9.03 (1H, s), 11.11 (1H, s).

- 15 (2) Ethyl 4-butoxy-2-neopentyl-1-oxo-1,2-dihydrobenzo{g}isoquinoline-3-carboxylate (synthesized according to the method similar to that in Example 1 (2))

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.96 (9H, s), 1.05 (3H, t,  $J=7.3$  Hz),  
20 1.48 (3H, t,  $J=7.1$  Hz), 1.55-1.66 (2H, m), 1.74-1.95 (2H, m), 4.06 (2H, t,  $J=6.4$  Hz), 4.11 (2H, bs), 4.46 (2H, q,  $J=7.1$  Hz), 7.52-7.67 (2H, m), 7.98-8.09 (2H, m), 8.24 (1H, s), 9.05 (1H, s).

- (3) 4-Butoxy-2-neopentyl-1-oxo-1,2-dihydrobenzo{g}isoquinoline-3-carboxylic acid  
25 (synthesized according to the method similar to that in Example 4 (3))

Melting point 203-205°C.

Elemental analysis for  $C_{23}H_{27}NO_4$

- 30 Calculated: C, 72.42; H, 7.13; N, 3.67.

Found: C, 72.39; H, 7.05; N, 3.53.

- $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.94 (9H, s), 1.03 (3H, t,  $J=7.1$  Hz),  
1.48-1.66 (2H, m), 1.79-1.93 (2H, m), 4.06 (2H, t,  $J=6.6$  Hz), 4.28 (2H, bs), 7.55-7.67 (2H, m), 7.74-7.82 (2H, m),  
35 8.03-8.08 (1H, m), 8.89 (1H, s).

(4) 4-Butoxy-3-hydroxymethyl-2-neopentyl-

benzo{g}isoquinolin-1(2H)-one (synthesized according to the method similar to that in Example 4 (4))

Melting point 147-148°C.

Elemental analysis for  $C_{23}H_{29}NO_3$

5 Calculated: C, 75.17; H, 7.95; N, 3.81.

Found: C, 75.12; H, 8.10; N, 3.65.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.98 (9H, s), 1.08 (3H, t, J=7.3 Hz),  
1.56-1.75 (2H, m), 1.86-1.99 (2H, m), 2.73 (1H, bs),  
3.97 (2H, t, J=6.6 Hz), 4.25 (2H, bs), 4.92 (2H, bs),  
10 7.45-7.57 (2H, m), 7.76-7.80 (1H, m), 7.91 (1H, s),  
7.94-7.99 (1H, m), 8.85 (1H, s).

(5) 4-Butoxy-3-chloromethyl-2-neopentyl-

benzo{g}isoquinolin-1(2H)-one (synthesized according to the method similar to that in Example 4 (5))

15  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.00 (9H, s), 1.08 (3H, t, J=7.2 Hz),  
1.57-1.76 (2H, m), 1.89-2.02 (2H, m), 4.05 (2H, t, J=6.5 Hz),  
4.21 (2H, bs), 4.95 (2H, bs), 7.50-7.66 (2H, m),  
7.98-8.09 (2H, m), 8.20 (1H, s), 9.04 (1H, s).

(6) 2-((4-Butoxy-2-neopentyl-1-oxo-1,2-dihydrobenzo{g}-  
20 isoquinolin-3-yl)methyl)-1H-isoindole-1,3(2H)-dione

(synthesized according to the method similar to that in Example 4 (6))

Melting point 244-245°C.

Elemental analysis for  $C_{31}H_{32}N_2O_4$

25 Calculated: C, 74.98; H, 6.50; N, 5.64.

Found: C, 74.73; H, 6.58; N, 5.60.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.02 (9H, s), 1.05 (3H, t, J=7.2 Hz),  
1.53-1.71 (2H, m), 1.90-2.04 (2H, m), 4.12 (2H, bs),  
4.15 (2H, t, J=6.8 Hz), 5.14 (2H, s), 7.48-7.64 (2H, m),  
30 7.68-7.83 (4H, m), 7.96-8.06 (2H, m), 8.21 (1H, s), 9.01 (1H, s).

(7) Tert-butyl (4-butoxy-2-neopentyl-1-oxo-1,2-dihydrobenzo{g}isoquinolin-3-yl)methylcarbamate

(synthesized according to the method similar to that in

35 Example 1 (6))

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.01 (9H, s), 1.07 (3H, t, J=7.3 Hz),

1.47 (9H, s), 1.50-1.73 (2H, m), 1.87-2.01 (2H, m), 3.96 (2H, t, J=6.4 Hz), 4.14 (2H, bs), 4.62 (2H, d, J=5.2 Hz), 4.73 (1H, bs), 7.48-7.64 (2H, m), 7.94-8.06 (2H, m), 8.11 (1H, s), 9.00 (1H, s).

- 5 (8) 3-(Aminomethyl)-4-butoxy-2-neopentylbenzo{g}isoquinolin-1(2H)-one hydrochloride (synthesized according to the method similar to that in Example 1 (7))  
Melting point 231-232°C.

10 Elemental analysis for  $C_{23}H_{31}N_2O_2Cl$

Calculated: C, 68.55; H, 7.55; N, 6.95.

Found: C, 68.30; H, 7.80; N, 7.02.

- $^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.93 (9H, s), 1.04 (3H, t, J=7.1 Hz), 1.56-1.67 (2H, m), 1.90-1.97 (2H, m), 4.05 (2H, bs),  
15 4.14 (2H, bs), 4.30 (2H, bs), 7.64-7.75 (2H, m), 8.19-8.27 (2H, m), 8.32 (1H, s), 8.63 (3H, bs), 8.99 (1H, s).

**Example 57**

3-(Aminomethyl)-4-butoxy-6-methoxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride

- 20 (1) Tert-butyl 4-hydroxy-2-neopentyl-6-fluoro-1-oxo-1,2-dihydro-3-isoquinoline-3-carboxylate (synthesized according to the method similar to that in Example 1 (1))

Melting point 130-131°C.

25 Elemental analysis for  $C_{19}H_{24}NO_4F$

Calculated: C, 65.31; H, 6.92; N, 4.01.

Found: C, 65.32; H, 7.19; N, 3.92.

- $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.86 (9H, s), 1.65 (9H, s), 4.51 (2H, bs), 7.30-7.40 (1H, m), 7.74 (1H, dd, J=2.6, 9.0 Hz),  
30 8.46 (1H, dd, J=5.4, 9.0 Hz), 10.68 (1H, s).

(2) Tert-butyl 4-butoxy-2-neopentyl-6-fluoro-1-oxo-1,2-dihydro-3-isoquinoline-3-carboxylate (synthesized according to the method similar to that in Example 1 (2))

- 35  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.97 (9H, s), 1.01 (3H, t, J=6.8 Hz), 1.49-1.60 (2H, m), 1.63 (9H, s), 1.73-1.86 (2H, m), 3.96

(2H, t, J=6.6 Hz), 4.00 (2H, bs), 7.18-7.27 (1H, m), 7.35 (1H, dd, J=2.4, 9.4 Hz), 8.43 (1H, dd, J=5.4, 8.8 Hz).

(3) A solution of tert-butyl 4-butoxy-2-neopentyl-6-fluoro-1-oxo-1,2-dihydro-3-isoquinoline-3-carboxylate (6.08 g, 15 mmol) in trifluoroacetic acid (20 ml) was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was recrystallized from ethyl acetate - n-hexane to give 4-butoxy-2-neopentyl-6-fluoro-1-oxo-1,2-dihydro-3-isoquinoline-3-carboxylic acid (4.98 g, 95.0%) as crystals.

Melting point 141-142°C.

Elemental analysis for  $C_{19}H_{24}NO_4F$

Calculated: C, 65.31; H, 6.92; N, 4.01.

Found: C, 65.38; H, 6.86; N, 3.90.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.95 (9H, s), 0.99 (3H, t, J=7.2 Hz), 1.48-1.60 (2H, m), 1.76-1.87 (2H, m), 4.02 (2H, t, J=6.5 Hz), 4.23 (2H, bs), 7.23-7.38 (2H, m), 8.43 (1H, dd, J=5.5, 9.1 Hz).

(4) A solution (8.68 g, 45 mmol) of 4-butoxy-2-neopentyl-6-fluoro-1-oxo-1,2-dihydro-3-isoquinoline-3-carboxylic acid (1.05 g, 3 mmol) and 20% sodium methoxide in methanol was refluxed under heating for 6 h. The reaction mixture was poured into water, and, after making the mixture acidic with 1N hydrochloric acid, extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from tetrahydrofuran - diethyl ether to give 4-butoxy-6-methoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinoline-3-carboxylic acid (0.96 g, 88.9%) as crystals.

Melting point 194-196°C.

Elemental analysis for  $C_{20}H_{27}NO_5$

Calculated: C, 66.46; H, 7.53; N, 3.88.

Found: C, 66.39; H, 7.45; N, 3.88.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.91 (9H, s), 1.01 (3H, t, J=7.2 Hz),  
1.51-1.62 (2H, m), 1.76-1.87 (2H, m), 3.91 (3H, s), 4.01  
(2H, t, J=6.4 Hz), 4.13 (2H, bs), 6.91 (1H, d, J=2.4 Hz),  
5 7.08 (1H, dd, J=2.4, 8.8 Hz), 8.17 (1H, d, J=8.8 Hz).

(5) 4-Butoxy-3-hydroxymethyl-6-methoxy-2-neopentyl-  
1(2H)-isoquinolinone (synthesized according to the  
method similar to that in Example 4 (4))

Melting point 124-125°C.

10 Elemental analysis for C<sub>20</sub>H<sub>29</sub>NO<sub>4</sub>

Calculated: C, 69.14; H, 8.41; N, 4.03.

Found: C, 69.06; H, 8.41; N, 3.96.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.94 (9H, s), 1.04 (3H, t, J=7.3 Hz),  
1.56-1.67 (2H, m), 1.79-1.93 (2H, m), 3.01 (1H, bs),  
15 3.89 (2H, t, J=6.2 Hz), 3.90 (3H, s), 4.17 (2H, bs),  
4.85 (2H, bs), 6.94-6.98 (2H, m), 8.15-8.21 (1H, m).

(6) 4-Butoxy-3-chloromethyl-6-methoxy-2-neopentyl-1(2H)-  
isoquinolinone (synthesized according to the method  
similar to that in Example 4 (5))

20 <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.98 (9H, s), 1.04 (3H, t, J=7.4 Hz),  
1.53-1.71 (2H, m), 1.82-1.95 (2H, m), 3.93 (3H, s), 3.96  
(2H, t, J=6.2 Hz), 4.24 (2H, bs), 4.88 (2H, bs), 7.07-  
7.30 (2H, m), 8.33-8.38 (1H, m).

(7) 2-((4-Butoxy-6-methoxy-2-neopentyl-1-oxo-1,2-  
25 dihydro-3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-  
dione (synthesized according to the method similar to  
that in Example 4 (6))

Melting point 145-146°C.

Elemental analysis for C<sub>28</sub>H<sub>32</sub>N<sub>2</sub>O<sub>5</sub>

30 Calculated: C, 70.57; H, 6.77; N, 5.88.

Found: C, 70.60; H, 6.83; N, 5.93.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.00 (9H, s), 1.01 (3H, t, J=7.3 Hz),  
1.51-1.66 (2H, m), 1.82-1.96 (2H, m), 3.92 (3H, s), 4.03  
(2H, t, J=6.7 Hz), 4.24 (2H, bs), 5.07 (2H, bs), 7.06  
35 (1H, dd, J=2.4, 8.8 Hz), 7.11 (1H, d, J=2.4 Hz), 7.63-  
7.83 (4H, m), 8.32 (1H, d, J=8.8 Hz).

(8) Tert-butyl (4-butoxy-6-methoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

5 Melting point 138.5-139°C.

Elemental analysis for  $C_{25}H_{38}N_2O_5$

Calculated: C, 67.24; H, 8.58; N, 6.27.

Found: C, 67.31; H, 8.85; N, 6.43.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (9H, s), 1.04 (3H, t,  $J=7.4$  Hz),  
10 1.45 (9H, s), 1.51-1.64 (2H, m), 1.79-1.93 (2H, m), 3.87  
(2H, t,  $J=6.4$  Hz), 3.93 (3H, s), 4.11 (2H, bs), 4.56 (2H,  
t,  $J=5.0$  Hz), 4.68 (1H, bs), 7.03-7.09 (2H, m), 8.33 (1H,  
d,  $J=9.6$  Hz).

(9) 3-(Aminomethyl)-4-butoxy-6-methoxy-2-neopentyl-  
15 1(2H)-1-oxo-isoquinolinone hydrochloride (synthesized  
according to the method similar to that in Example 1  
(7))

Melting point 172-174°C.

Elemental analysis for  $C_{20}H_{31}N_2O_3Cl \cdot 1/4H_2O$

20 Calculated: C, 62.00; H, 8.20; N, 7.23.

Found: C, 61.90; H, 8.11; N, 7.35.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.90 (9H, s), 1.00 (3H, t,  $J=7.1$  Hz),  
1.52-1.64 (2H, m), 1.77-1.92 (2H, m), 3.93 (3H, s), 3.94  
(2H, t,  $J=6.4$  Hz), 4.08 (2H, bs), 4.23 (2H, bs), 7.09  
25 (1H, d,  $J=2.4$  Hz), 7.20 (1H, dd,  $J=2.4, 8.8$  Hz), 8.20  
(1H, d,  $J=8.8$  Hz), 8.59 (3H, bs).

#### Example 58

3-(Aminomethyl)-6-benzyloxy-4-butoxy-2-neopentyl-1(2H)-  
isoquinolinone hydrochloride

30 (1) 6-Benzyloxy-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-  
3-isoquinoline-3-carboxylic acid (synthesized according  
to the method similar to that in Example 57 (4))

Melting point 163-164°C.

Elemental analysis for  $C_{26}H_{31}NO_5$

35 Calculated: C, 71.37; H, 7.14; N, 3.20.

Found: C, 71.13; H, 7.10; N, 2.94.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.89 (9H, s), 0.99 (3H, t, J=7.1 Hz), 1.41-1.59 (2H, m), 1.69-1.84 (2H, m), 3.91 (2H, t, J=6.4 Hz), 4.13 (2H, bs), 5.17 (2H, s), 7.01 (1H, d, J=2.4 Hz), 7.18 (1H, dd, J=2.4, 9.0 Hz), 7.33-7.44 (5H, m), 8.22

(1H, d, J=9.0 Hz).

(2) 6-Benzyloxy-4-butoxy-3-hydroxymethyl-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))  
Melting point: 95-95.5°C.

10 Elemental analysis for C<sub>26</sub>H<sub>33</sub>NO<sub>4</sub>  
Calculated: C, 73.73; H, 7.85; N, 3.31.  
Found: C, 73.44; H, 7.77; N, 3.38.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.95 (9H, s), 1.02 (3H, t, J=7.4 Hz),

1.45-1.64 (2H, m), 1.73-1.86 (2H, m), 2.57 (1H, bs),

15 3.80 (2H, t, J=6.4 Hz), 4.18 (2H, bs), 4.84 (2H, bs), 5.18 (2H, s), 7.06-7.11 (2H, m), 7.31-7.47 (5H, m), 8.23 (1H, d, J=8.0 Hz).

(3) 6-Benzyloxy-4-butoxy-3-chloromethyl-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the

20 method similar to that in Example 4 (5))

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.97 (9H, s), 1.03 (3H, t, J=7.1 Hz),

1.46-1.65 (2H, m), 1.74-1.88 (2H, m), 3.84 (2H, t, J=6.4

Hz), 4.14 (2H, bs), 4.86 (2H, bs), 5.21 (2H, s), 7.12-7.48 (7H, m), 8.36 (1H, d, J=9.2 Hz).

25 (4) 2-((6-Benzyloxy-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

Elemental analysis for C<sub>34</sub>H<sub>36</sub>N<sub>2</sub>O<sub>5</sub> 1/2H<sub>2</sub>O

30 Calculated: C, 72.71; H, 6.64; N, 4.99.

Found: C, 72.74; H, 6.42; N, 5.26.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.99 (3H, t, J=7.3 Hz), 1.00 (9H, s),

1.39-1.58 (2H, m), 1.64-1.89 (2H, m), 3.92 (2H, t, J=6.7

Hz), 4.10 (2H, bs), 5.06 (2H, bs), 5.20 (2H, s), 7.11-

35 7.17 (2H, m), 7.31-7.47 (5H, m), 7.70-7.90 (4H, m), 8.30-8.35 (1H, m).



(5) Tert-butyl (6-benzyloxy-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1

(6))

5 Melting point 114-115°C.

Elemental analysis for  $C_{31}H_{42}N_2O_5$

Calculated: C, 71.42; H, 8.10; N, 5.36.

Found: C, 71.34; H, 8.40; N, 5.39.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.98 (9H, s), 1.02 (3H, t,  $J=7.4$  Hz),

10 1.45 (9H, s), 1.46-1.59 (2H, m), 1.73-1.87 (2H, m), 3.76 (2H, t,  $J=6.4$  Hz), 4.11 (2H, bs), 4.54 (2H, d,  $J=5.2$  Hz), 4.66 (1H, bs), 5.21 (2H, s), 7.08 (1H, d,  $J=2.6$  Hz), 7.14 (1H, dd,  $J=2.6, 8.8$  Hz), 7.32-7.48 (5H, m), 8.33 (1H, d,  $J=8.8$  Hz).

15 (6) 3-(Aminomethyl)-6-benzyloxy-4-butoxy-2-neopentyl-1(2H)-1-oxo-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 234-236°C.

20 Elemental analysis for  $C_{26}H_{35}N_2O_3Cl$

Calculated: C, 68.03; H, 7.69; N, 6.10.

Found: C, 67.96; H, 7.64; N, 5.93.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.89 (9H, s), 0.98 (3H, t,  $J=7.5$  Hz),

1.45-1.56 (2H, m), 1.71-1.82 (2H, m), 3.84 (2H, t,  $J=6.2$  Hz), 4.07 (2H, bs), 4.21 (2H, bs), 5.33 (2H, bs), 7.11 (1H, d,  $J=2.2$  Hz), 7.27 (1H, dd,  $J=2.2, 8.8$  Hz), 7.34-7.50 (5H, m), 8.19 (1H, d,  $J=8.8$  Hz), 8.52 (3H, bs).

#### Example 59

3-(Aminomethyl)-4-butoxy-6-hydroxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride

30 (1) A suspension of tert-butyl (6-benzyloxy-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (2.61 g, 5 mmol) and 5% palladium carbon (1.5 g) in tetrahydrofuran (10 ml) and ethanol (10 ml) was stirred under a hydrogen atmosphere at room temperature for 2 h. After filtering off 5%

palladium carbon, the filtrate was concentrated under reduced pressure. The residue was recrystallized from ethyl acetate - n-hexane to give tert-butyl (4-butoxy-6-hydroxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)-methylcarbamate (4.98 g, 95.0%) as crystals.  
Melting point 195.5-197°C.

Elemental analysis for  $C_{24}H_{36}N_2O_5$

Calculated: C, 66.64; H, 8.39; N, 6.48.

Found: C, 66.57; H, 8.58; N, 6.49.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.96 (3H, t, J=7.4 Hz), 0.99 (9H, s), 1.45 (9H, s), 1.46-1.55 (2H, m), 1.72-1.81 (2H, m), 3.82 (2H, t, J=6.6 Hz), 4.11 (2H, bs), 4.56 (2H, d, J=5.2 Hz), 4.78 (1H, bs), 7.06-7.11 (2H, m), 8.26 (1H, d, J=9.2 Hz), 8.79 (1H, bs).

(2) 3-(Aminomethyl)-4-butoxy-6-hydroxy-2-neopentyl-1(2H)-1-oxo-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 264-266°C.

Elemental analysis for  $C_{19}H_{29}N_2O_3Cl \cdot 1/4H_2O$

Calculated: C, 61.11; H, 7.96; N, 7.50.

Found: C, 61.22; H, 7.77; N, 7.56.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.89 (9H, s), 1.00 (3H, t, J=7.1 Hz), 1.50-1.61 (2H, m), 1.77-1.92 (2H, m), 3.89 (2H, t, J=6.2 Hz), 4.05 (2H, bs), 4.20 (2H, bs), 7.03-7.08 (2H, m), 8.11 (1H, d, J=8.2 Hz), 8.50 (1H, s), 10.67 (1H, bs).

#### Example 60

3-(Aminomethyl)-4-butoxy-2-neopentyl-6-propoxy-1(2H)-isoquinolinone hydrochloride

(1) A solution of tert-butyl (4-butoxy-6-hydroxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.52 g, 1.2 mmol), 1-bromopropane (0.16 ml, 1.2 mmol) and potassium carbonate (0.16 g, 1.2 mmol) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 12 h. The reaction mixture was poured into water and extracted with ethyl

acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl (4-butoxy-2-neopentyl-1-oxo-6-propoxy-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.50 g, 89.3%) as an amorphous.

Elemental analysis for  $C_{27}H_{42}N_2O_5 \cdot 1/4H_2O$

Calculated: C, 67.68; H, 8.94; N, 5.85.

10 Found: C, 67.87; H, 8.89; N, 5.95.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (9H, s), 1.04 (3H, t,  $J=7.2$  Hz), 1.08 (3H, t,  $J=7.4$  Hz), 1.45 (9H, s), 1.50-1.65 (2H, m), 1.79-1.93 (4H, m), 3.83 (2H, t,  $J=6.6$  Hz), 4.01 (2H, bs), 4.04 (2H, t,  $J=6.4$  Hz), 4.55 (2H, d,  $J=5.2$  Hz), 4.67 (1H, bs), 7.02-7.08 (2H, m), 8.31 (1H, d,  $J=9.6$  Hz).

(2) 3-(Aminomethyl)-4-butoxy-2-neopentyl-6-propoxy-1(2H)-1-oxo-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

20 Melting point 202-204°C.

Elemental analysis for  $C_{22}H_{35}N_2O_3Cl$

Calculated: C, 64.29; H, 8.58; N, 6.82.

Found: C, 64.05; H, 8.29; N, 6.64.

25  $^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.90 (9H, s), 1.00 (3H, t,  $J=7.4$  Hz), 1.02 (3H, t,  $J=7.3$  Hz), 1.53-1.63 (2H, m), 1.72-1.86 (4H, m), 3.94 (2H, t,  $J=6.2$  Hz), 4.07 (2H, bs), 4.10 (2H, t,  $J=6.5$  Hz), 4.23 (2H, bs), 7.07 (1H, d,  $J=2.5$  Hz), 7.19 (1H, dd,  $J=2.5, 8.8$  Hz), 8.18 (1H, d,  $J=8.8$  Hz), 8.51 (3H, bs).

30 Example 61

3-(Aminomethyl)-4,6-dibutoxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride

(1) Tert-butyl (4,6-dibutoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 60 (1))

Elemental analysis for  $C_{28}H_{44}N_2O_5$

Calculated: C, 68.82; H, 9.08; N, 5.73.

Found: C, 68.66; H, 8.87; N, 5.54.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (9H, s), 1.00 (3H, t,  $J=7.4$  Hz),

5 1.04 (3H, t,  $J=7.0$  Hz), 1.45 (9H, s), 1.51-1.64 (4H, m),  
1.77-1.90 (4H, m), 3.86 (2H, t,  $J=6.4$  Hz), 4.08 (2H, t,  
 $J=6.5$  Hz), 4.14 (2H, bs), 4.56 (2H, d,  $J=5.2$  Hz), 4.67  
(1H, bs), 7.02-7.08 (2H, m), 8.32 (1H, d,  $J=9.4$  Hz).

(2) 3-(Aminomethyl)-4,6-dibutoxy-2-neopentyl-1(2H)-1-  
10 oxo-isoquinolinone hydrochloride (synthesized according  
to the method similar to that in Example 1 (7))  
Melting point 184-186°C.

Elemental analysis for  $C_{23}H_{37}N_2O_3Cl \cdot 3/4H_2O$

Calculated: C, 63.00; H, 8.85; N, 6.39.

15 Found: C, 62.85; H, 8.88; N, 6.14.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.90 (9H, s), 0.96 (3H, t,  $J=7.8$  Hz),  
1.00 (3H, t,  $J=7.4$  Hz), 1.42-1.60 (4H, m), 1.63-1.92 (4H,  
m), 3.94 (2H, t,  $J=6.2$  Hz), 4.11 (2H, bs), 4.15 (2H, t,  
 $J=6.5$  Hz), 4.23 (2H, bs), 7.07 (1H, d,  $J=2.4$  Hz), 7.18  
20 (1H, dd,  $J=2.4, 8.8$  Hz), 8.18 (1H, d,  $J=8.8$  Hz), 8.57  
(3H, bs).

#### Example 62

3-(Aminomethyl)-4-butoxy-6-(2-methoxyethoxy)-2-  
neopentyl-1(2H)-isoquinolinone hydrochloride

25 (1) Tert-butyl {4-butoxy-6-(2-methoxyethoxy)-2-  
neopentyl-1-oxo-1,2-dihydro-3-  
isoquinolinyl}methylcarbamate (synthesized according to  
the method similar to that in Example 60 (1))

Elemental analysis for  $C_{27}H_{42}N_2O_6$

30 Calculated: C, 66.10; H, 8.63; N, 5.71.

Found: C, 66.22; H, 8.59; N, 5.41.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (9H, s), 1.03 (3H, t,  $J=7.4$  Hz),

1.45 (9H, s), 1.52-1.64 (2H, m), 1.78-1.89 (2H, m), 3.49  
(3H, s), 3.80-3.88 (4H, m), 4.20 (2H, bs), 4.22-4.25 (2H,  
35 m), 4.55 (2H, d,  $J=5.4$  Hz), 4.66 (1H, bs), 7.08-7.13 (2H,  
m), 8.30-8.35 (1H, m).

(2) 3-(Aminomethyl)-4-butoxy-6-(2-methoxyethoxy)-2-neopentyl-1(2H)-1-oxo-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

5 Melting point 188-189°C.

Elemental analysis for  $C_{22}H_{35}N_2O_4Cl$

Calculated: C, 61.89; H, 8.26; N, 6.56.

Found: C, 61.55; H, 8.34; N, 6.59.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.90 (9H, s), 1.00 (3H, t,  $J=7.3$  Hz),  
10 1.51-1.62 (2H, m), 1.77-1.88 (2H, m), 3.33 (3H, s),  
3.71-3.75 (2H, m), 3.94 (2H, t,  $J=6.4$  Hz), 4.07 (2H, bs),  
4.25-4.30 (4H, m), 7.09 (1H, d,  $J=2.4$  Hz), 7.21 (1H, dd,  
 $J=2.4$ , 8.8 Hz), 8.18 (1H, d,  $J=8.8$  Hz), 8.55 (3H, bs).

#### Example 63

15 3-(Aminomethyl)-7-benzyloxy-4-butoxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride

(1) A solution of 5-benzyloxy-2-(ethoxycarbonyl)benzoic acid (21.86 g, 120 mmol), ethyl 2-

(neopentylamino)acetate (20.79 g, 120 mmol), 1-ethyl-3-

20 (3-dimethylaminopropyl)carbodiimide hydrochloride (28.76

g, 150 mmol) and 1-hydroxybenzotriazole (22.97 g, 150

mmol) in N,N-dimethylformamide (200 ml) was stirred at

room temperature for 3 h. The reaction mixture was

poured into water and extracted with ethyl acetate. The

25 extract was washed with brine, dried over anhydrous

magnesium sulfate and concentrated under reduced

pressure. The residue was dissolved in N,N-

dimethylformamide (300 ml), and potassium carbonate

(33.17 g, 240 mmol) and benzyl bromide (35.7 ml, 300

30 mmol) were added. The mixture was stirred at room

temperature for 12 h. The reaction mixture was poured

into water and extracted with ethyl acetate. The

extract was washed with brine, dried over anhydrous

magnesium sulfate and concentrated under reduced

35 pressure. The residue was dissolved in ethanol (50 ml)

and 20% sodium ethoxide ethanol solution (34.04 g, 100

mmol) was added. The mixture was stirred at room temperature for 1 h. The reaction mixture was poured into 1N hydrochloric acid (150 ml) and extracted with ethyl acetate. The extract was washed with brine, dried  
5 over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography and the component eluted earlier was concentrated to give ethyl 7-benzyloxy-4-hydroxy-2-neopentyl-1-oxo-1,2-dihydro-3-  
10 isoquinolinecarboxylate as an oil. To a solution of the obtained ethyl 7-benzyloxy-4-hydroxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (3.26 g, 8 mmol), 1-butanol (1.1 ml, 12 mmol) and tributylphosphine (4.0 ml, 16 mmol) in tetrahydrofuran (30 ml) was added 1,1'-  
15 (azodicarbonyl)dipiperidine (4.04 g, 16 mmol) and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to give ethyl 7-benzyloxy-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate  
20 (3.61 g, 97.0%) as an oil.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.94 (9H, s), 1.00 (3H, t, J=7.4 Hz), 1.43 (3H, t, J=7.2 Hz), 1.51-1.66 (2H, m), 1.73-1.87 (2H, m), 3.94 (2H, t, J=6.5 Hz), 4.14 (2H, bs), 4.42 (2H, q, J=7.2 Hz), 5.20 (2H, bs), 7.34-7.50 (6H, m), 7.73 (1H, d, J=8.8 Hz), 7.96 (1H, d, J=2.6 Hz).

(2) 7-Benzyloxy-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinoline-3-carboxylic acid (synthesized according to the method similar to that in Example 57 (4))

30 Elemental analysis for C<sub>26</sub>H<sub>31</sub>NO<sub>5</sub>

Calculated: C, 71.37; H, 7.14; N, 3.20.

Found: C, 71.11; H, 7.35; N, 3.08.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.91 (9H, s), 0.95 (3H, t, J=7.4 Hz), 1.44-1.59 (2H, m), 1.74-1.89 (2H, m), 4.00 (2H, t, J=6.6  
35 Hz), 4.35 (2H, bs), 5.20 (2H, s), 7.31-7.51 (6H, m), 7.60 (1H, d, J=8.8 Hz), 7.84 (1H, d, J=2.6 Hz).

(3) 7-Benzyloxy-4-butoxy-3-hydroxymethyl-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))  
Melting point 156.5-157°C.

5 Elemental analysis for  $C_{26}H_{33}NO_4$

Calculated: C, 73.73; H, 7.85; N, 3.31.

Found: C, 73.76; H, 7.62; N, 3.42.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.98 (9H, s), 1.00 (3H, t,  $J=7.4$  Hz),  
1.47-1.64 (2H, m), 1.76-1.90 (2H, m), 2.57 (1H, bs),  
10 3.87 (2H, t,  $J=6.4$  Hz), 4.23 (2H, bs), 4.86 (2H, bs),  
5.17 (2H, s), 7.25-7.51 (6H, m), 7.59 (1H, d,  $J=8.8$  Hz),  
7.82 (1H, d,  $J=2.2$  Hz).

(4) 7-Benzyloxy-4-butoxy-3-chloromethyl-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the  
15 method similar to that in Example 4 (5))

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (9H, s), 1.03 (3H, t,  $J=7.4$  Hz),  
1.54-1.69 (2H, m), 1.80-1.94 (2H, m), 3.94 (2H, t,  $J=6.4$   
Hz), 4.17 (2H, bs), 4.90 (2H, bs), 5.20 (2H, s), 7.33-  
7.50 (6H, m), 7.69 (1H, d,  $J=8.8$  Hz), 7.96 (1H, d,  $J=2.4$   
20 Hz).

(5) 2-((7-Benzyloxy-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

25 Melting point 120-121°C.

Elemental analysis for  $C_{34}H_{36}N_2O_5$

Calculated: C, 73.89; H, 6.57; N, 5.07.

Found: C, 73.77; H, 6.28; N, 5.29.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.00 (3H, t,  $J=7.2$  Hz), 1.02 (9H, s),  
30 1.44-1.62 (2H, m), 1.81-1.95 (2H, m), 4.02 (2H, t,  $J=6.8$   
Hz), 4.06 (2H, bs), 5.08 (2H, bs), 5.18 (2H, s), 7.30-  
7.50 (6H, m), 7.67-7.90 (5H, m), 7.93 (1H, d,  $J=2.6$  Hz).

(6) Tert-butyl (7-benzyloxy-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized  
35 according to the method similar to that in Example 1  
(6))

Melting point 122-123°C.

Elemental analysis for  $C_{31}H_{42}N_2O_5$

Calculated: C, 71.42; H, 8.10; N, 5.36.

Found: C, 71.31; H, 8.19; N, 5.39.

- 5  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.00 (9H, s), 1.02 (3H, t,  $J=7.2$  Hz), 1.45 (9H, s), 1.46-1.64 (2H, m), 1.78-1.92 (2H, m), 3.86 (2H, t,  $J=6.6$  Hz), 4.17 (2H, bs), 4.56 (2H, t,  $J=5.2$  Hz), 4.65 (1H, bs), 5.19 (2H, s), 7.30-7.50 (6H, m), 7.64 (1H, d,  $J=8.6$  Hz), 7.93 (1H, d,  $J=2.6$  Hz).

- 10 (7) 3-(Aminomethyl)-7-benzyloxy-4-butoxy-2-neopentyl-1(2H)-1-oxo-isoquinoline hydrochloride (synthesized according to the method similar to that in Example 1 (7)).

Melting point 202-204°C.

- 15 Elemental analysis for  $C_{26}H_{35}N_2O_3Cl \cdot H_2O$

Calculated: C, 65.46; H, 7.82; N, 5.87.

Found: C, 65.57; H, 7.47; N, 5.49.

- $^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.91 (9H, s), 0.99 (3H, t,  $J=7.3$  Hz), 1.48-1.60 (2H, m), 1.76-1.91 (2H, m), 3.92 (2H, t,  $J=6.4$  Hz), 4.08 (2H, bs), 4.23 (2H, bs), 5.27 (2H, s), 7.31-7.55 (6H, m), 7.74 (1H, d,  $J=8.6$  Hz), 7.80 (1H, d,  $J=2.6$  Hz), 8.51 (3H, bs).
- 20

#### Example 64

3-(Aminomethyl)-4-butoxy-7-hydroxy-2-neopentyl-1(2H)-

- 25 isoquinolinone hydrochloride

(1) Tert-butyl (4-butoxy-7-hydroxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 59 (1))

- 30 Melting point 237-238°C.

Elemental analysis for  $C_{24}H_{36}N_2O_5$

Calculated: C, 66.64; H, 8.39; N, 6.48.

Found: C, 66.54; H, 8.41; N, 6.36.

- $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.88 (9H, s), 0.96 (3H, t,  $J=7.2$  Hz), 1.40 (2H, m), 1.44-1.59 (9H, s), 1.40-1.55 (2H, m), 1.69-1.79 (2H, m), 3.80 (2H, t,  $J=6.2$  Hz), 3.94 (2H, bs),
- 35



4.39 (2H, d, J=4.8 Hz), 7.21 (1H, bs), 7.24 (1H, dd, J=2.4, 8.4 Hz), 7.56 (1H, d, J=2.4 Hz), 7.58 (1H, d, J=8.4 Hz), 10.15 (1H, s).

- (2) 3-(Aminomethyl)-4-butoxy-7-hydroxy-2-neopentyl-1(2H)-1-oxo-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 238-239°C.

Elemental analysis for  $C_{19}H_{29}N_2O_3Cl$

- 10 Calculated: C, 61.86; H, 7.92; N, 7.59.

Found: C, 61.80; H, 7.84; N, 7.52.

- $^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.89 (9H, s), 0.98 (3H, t, J=7.3 Hz), 1.44-1.63 (2H, m), 1.75-1.89 (2H, m), 3.91 (2H, t, J=6.5 Hz), 4.08 (2H, bs), 4.20 (2H, bs), 7.31 (1H, dd, J=2.8, 8.6 Hz), 7.62 (1H, d, J=2.8 Hz), 7.64 (1H, d, J=8.6 Hz), 8.43 (3H, bs), 10.33 (1H, s).

#### Example 65

3-(Aminomethyl)-4-butoxy-7-methoxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride

- 20 (1) Tert-butyl (4-butoxy-7-methoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 60 (1))

Melting point 171-172°C.

- 25 Elemental analysis for  $C_{25}H_{38}N_2O_5 \cdot 1/4H_2O$

Calculated: C, 66.57; H, 8.60; N, 6.21.

Found: C, 66.65; H, 8.77; N, 6.15.

- $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.00 (9H, s), 1.02 (3H, t, J=7.4 Hz), 1.45 (9H, s), 1.51-1.66 (2H, m), 1.78-1.92 (2H, m), 3.86 (2H, t, J=6.4 Hz), 3.93 (3H, s), 4.14 (2H, bs), 4.56 (2H, d, J=4.8 Hz), 4.66 (1H, bs), 7.28 (1H, dd, J=2.6, 8.8 Hz), 7.63 (1H, d, J=8.8 Hz), 7.82 (1H, d, J=2.6 Hz).

- (2) 3-(Aminomethyl)-4-butoxy-7-methoxy-2-neopentyl-1(2H)-1-oxo-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 210-212°C.

Elemental analysis for  $C_{20}H_{31}N_2O_3Cl$

Calculated: C, 62.00; H, 8.20; N, 7.23.

Found: C, 61.97; H, 8.07; N, 7.28.

- <sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.91 (9H, s), 0.99 (3H, t, J=7.3 Hz), 1.45-1.64 (2H, m), 1.77-1.91 (2H, m), 3.90 (3H, s), 3.92 (2H, t, J=6.2 Hz), 4.10 (2H, bs), 4.23 (2H, bs), 7.45 (1H, dd, J=2.6, 8.8 Hz), 7.70 (1H, d, J=2.6 Hz), 7.73 (1H, d, J=8.8 Hz), 8.52 (3H, bs).

10 **Example 66**

3-(Aminomethyl)-4-butoxy-7-ethoxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride

(1) Tert-butyl (4-butoxy-7-ethoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized

- 15 according to the method similar to that in Example 60 (1))

Melting point 140-142°C.

Elemental analysis for  $C_{26}H_{40}N_2O_5$

Calculated: C, 67.80; H, 8.75; N, 6.08.

- 20 Found: C, 67.57; H, 8.51; N, 6.10.

- <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.00 (9H, s), 1.02 (3H, t, J=7.4 Hz), 1.44 (9H, s), 1.45 (3H, t, J=7.0 Hz), 1.49-1.67 (2H, m), 1.78-1.92 (2H, m), 3.85 (2H, t, J=6.6 Hz), 4.11 (2H, bs), 4.16 (2H, q, J=7.0 Hz), 4.56 (2H, d, J=5.2 Hz), 4.65 (1H, bs), 7.27 (1H, dd, J=2.4, 8.8 Hz), 7.62 (1H, d, J=8.8 Hz), 7.80 (1H, d, J=2.4 Hz).

(2) 3-(Aminomethyl)-4-butoxy-7-ethoxy-2-neopentyl-1(2H)-1-oxo-isoquinolinone hydrochloride (synthesized

according to the method similar to that in Example 1

- 30 (7))

Elemental analysis for  $C_{21}H_{33}N_2O_3Cl \cdot 1/2H_2O$

Calculated: C, 62.13; H, 8.44; N, 6.90.

Found: C, 62.21; H, 8.40; N, 7.15.

- <sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.91 (9H, s), 0.99 (3H, t, J=7.3 Hz), 1.38 (3H, t, J=6.8 Hz), 1.49-1.60 (2H, m), 1.69-1.92 (2H, m), 3.92 (2H, bs), 4.12-4.22 (6H, m), 7.44 (1H, dd,

J=2.6, 8.8 Hz), 7.62-7.75 (2H, m), 8.54 (3H, bs).

**Example 67**

3-(Aminomethyl)-4-butoxy-2-neopentyl-7-propoxy-1(2H)-isoquinolinone hydrochloride

- 5 (1) Tert-butyl (4-butoxy-2-neopentyl-1-oxo-7-propoxy-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 60 (1)).

Melting point 143.5-144.5°C.

- 10 Elemental analysis for  $C_{27}H_{42}N_2O_5$

Calculated: C, 68.32; H, 8.92; N, 5.90.

Found: C, 68.30; H, 8.95; N, 6.02.

- $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.00 (9H, s), 1.02 (3H, t, J=7.4 Hz),  
1.06 (3H, t, J=7.4 Hz), 1.45 (9H, s), 1.51-1.65 (2H, m),  
15 1.76-1.92 (4H, m), 3.85 (2H, t, J=6.6 Hz), 4.06 (2H, t, J=6.8 Hz), 4.09 (2H, bs), 4.56 (2H, d, J=4.4 Hz), 4.62 (1H, bs), 7.28 (1H, dd, J=2.7, 8.8 Hz), 7.62 (1H, d, J=8.8 Hz), 7.80 (1H, d, J=2.7 Hz).

- (2) 3-(Aminomethyl)-4-butoxy-2-neopentyl-7-propoxy-1(2H)-1-oxo-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7)).

Melting point 216-218°C.

Elemental analysis for  $C_{22}H_{35}N_2O_3Cl \cdot 1/4H_2O$

- 25 Calculated: C, 63.60; H, 8.61; N, 6.74.

Found: C, 63.84; H, 8.67; N, 6.80.

- $^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.90 (9H, s), 0.99 (3H, t, J=7.4 Hz),  
1.01 (3H, t, J=7.3 Hz), 1.49-1.70 (2H, m), 1.73-1.90 (4H, m),  
3.92 (2H, t, J=6.6 Hz), 4.07 (2H, t, J=6.4 Hz), 4.10  
30 (2H, bs), 4.23 (2H, bs), 7.45 (1H, dd, J=2.8, 8.8 Hz), 7.68 (1H, d, J=2.8 Hz), 7.72 (1H, d, J=8.8 Hz), 8.51 (3H, bs).

**Example 68**

3-(Aminomethyl)-4,7-dibutoxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride

- 35 (1) Tert-butyl (4-butoxy-7-butoxy-2-neopentyl-1-oxo-1,2-

dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 60 (1))

Elemental analysis for  $C_{28}H_{44}N_2O_5$

5 Calculated: C, 68.82; H, 9.08; N, 5.73.

Found: C, 68.79; H, 9.34; N, 5.72.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (3H, t,  $J=7.2$  Hz), 1.00 (9H, s), 1.02 (3H, t,  $J=7.2$  Hz), 1.45 (9H, s), 1.46-1.64 (4H, m), 1.74-1.89 (4H, m), 3.85 (2H, t,  $J=6.4$  Hz), 4.07 (2H, bs), 10 4.10 (2H, t,  $J=6.4$  Hz), 4.55 (2H, d,  $J=4.4$  Hz), 4.61 (1H, bs), 7.28 (1H, dd,  $J=2.8, 8.8$  Hz), 7.62 (1H, d,  $J=8.8$  Hz), 7.80 (1H, d,  $J=2.8$  Hz).

(2) 3-(Aminomethyl)-4,7-dibutoxy-2-neopentyl-1(2H)-1-oxo-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 192.5-193°C.

Elemental analysis for  $C_{23}H_{37}N_2O_3Cl \cdot 1/4H_2O$

Calculated: C, 64.32; H, 8.80; N, 6.52.

Found: C, 64.38; H, 8.83; N, 6.49.

20  $^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.91 (9H, s), 0.95-1.02 (6H, m), 1.41-1.60 (4H, m), 1.68-1.87 (4H, m), 3.92 (2H, t,  $J=6.1$  Hz), 4.11 (2H, t,  $J=6.2$  Hz), 4.14 (2H, bs), 4.23 (2H, bs), 7.44 (1H, dd,  $J=2.6, 8.8$  Hz), 7.68 (1H, d,  $J=2.6$  Hz), 7.72 (1H, d,  $J=8.8$  Hz), 8.54 (3H, bs).

## 25 Example 69

3-(Aminomethyl)-4-butoxy-5,6-dimethoxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride

(1) A solution of ethyl 6-formyl-2,3-dimethoxybenzoate (5.24 g, 22 mmol), sodium dihydrogen phosphate (3.60 g, 30 mmol) and 2-methyl-2-butene (10.3 ml, 96.8 mmol) in 30 t-butanol (20 ml), tetrahydrofuran (20 ml) and water (20 ml) was stirred at room temperature for 10 min. To the obtained mixture was added sodium chlorite (6.76 g, 74.8 mmol) and the mixture was stirred at room temperature 35 for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed

with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate - n-hexane to give 2-(ethoxycarbonyl)-3,4-dimethoxybenzoic acid (4.51 g, 80.7%) as crystals.

Melting point 148-149°C.

Elemental analysis for  $C_{12}H_{14}O_6$

Calculated: C, 56.69; H, 5.55.

Found: C, 56.52; H, 5.64.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.38 (3H, t,  $J=7.2$  Hz), 3.87 (3H, s), 3.95 (3H, s), 4.43 (2H, q,  $J=7.2$  Hz), 6.97 (1H, d,  $J=8.8$  Hz), 7.88 (1H, d,  $J=8.8$  Hz).

(2) A solution of 2-(ethoxycarbonyl)-3,4-dimethoxybenzoic acid (4.45 g, 17.5 mmol), ethyl 2-(neopentylamino)acetate (3.47 g, 20 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (3.83 g, 20 mmol) in N,N-dimethylformamide (50 ml) was stirred at room temperature for 3 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in ethanol (50 ml) and 20% sodium ethoxide ethanol solution (34.04 g, 100 mmol) was added thereto. The mixture was stirred at room temperature for 1 h. The reaction mixture was poured into 1N hydrochloric acid (150 ml) and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give ethyl 5,6-dimethoxy-4-hydroxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (3.21 g, 50.6%) as an oil.

Elemental analysis for  $C_{19}H_{25}NO_6 \cdot 1/2H_2O$

Calculated: C, 61.28; H, 7.04; N, 3.76.

Found: C, 61.61; H, 6.67; N, 3.85.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.90 (9H, s), 1.43 (3H, t,  $J=7.2$  Hz),

4.01 (3H, s), 4.04 (3H, s), 4.21 (2H, bs), 4.44 (2H, q, J=7.2 Hz), 7.24 (1H, d, J=9.2 Hz), 8.28 (1H, d, J=9.2 Hz), 9.56 (1H, s).

(3) Ethyl 4-butoxy-5,6-dimethoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))

Melting point 70-71°C.

Elemental analysis for  $C_{23}H_{33}NO_6$

Calculated: C, 65.85; H, 7.93; N, 3.34.

10 Found: C, 65.64; H, 7.79; N, 3.45.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.95 (9H, s), 0.96 (3H, t, J=7.2 Hz), 1.34-1.52 (5H, m), 1.65-1.80 (2H, m), 3.63 (3H, s), 3.89-3.96 (4H, m), 4.00 (3H, s), 4.42 (2H, q, J=7.2 Hz), 7.19 (1H, d, J=8.8 Hz), 8.28 (1H, d, J=8.8 Hz).

15 (4) 4-Butoxy-5,6-dimethoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 144-145.5°C.

20 Elemental analysis for  $C_{21}H_{29}NO_6 \cdot 1/4H_2O$

Calculated: C, 63.70; H, 7.51; N, 3.54.

Found: C, 63.81; H, 7.28; N, 3.60.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.91 (9H, s), 0.95 (3H, t, J=7.2 Hz), 1.37-1.52 (2H, m), 1.72-1.86 (2H, m), 3.87 (3H, s), 3.89-3.97 (2H, m), 4.00 (3H, s), 4.10 (2H, bs), 7.22 (1H, d, J=8.9 Hz), 8.27 (1H, d, J=8.9 Hz).

(5) 4-Butoxy-5,6-dimethoxy-3-hydroxymethyl-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

30 Melting point 140-141°C.

Elemental analysis for  $C_{21}H_{31}NO_5 \cdot 1/4H_2O$

Calculated: C, 66.03; H, 8.31; N, 3.67.

Found: C, 66.13; H, 8.22; N, 3.77.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.97 (9H, s), 1.00 (3H, t, J=7.2 Hz), 1.46-1.64 (2H, m), 1.75-1.80 (2H, m), 2.39 (1H, s), 3.84 (3H, s), 3.86 (2H, t, J=7.0 Hz), 3.98 (3H, s), 4.17 (2H,

bs), 4.86 (2H, bs), 7.11 (1H, d, J=9.0 Hz), 8.20 (1H, d, J=9.0 Hz).

(6) 4-Butoxy-3-chloromethyl-5,6-dimethoxy-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5)).

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.98 (9H, s), 1.02 (3H, t, J=7.4 Hz), 1.47-1.64 (2H, m), 1.76-1.87 (2H, m), 3.85 (3H, s), 3.89 (2H, t, J=6.2 Hz), 3.99 (3H, s), 4.12 (2H, bs), 4.92 (2H, bs), 7.24 (1H, d, J=8.8 Hz), 8.28 (1H, d, J=8.8 Hz).

(7) 2-[(4-Butoxy-5,6-dimethoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6)).

Melting point 122-123°C.

Elemental analysis for  $\text{C}_{29}\text{H}_{34}\text{N}_2\text{O}_6$

Calculated: C, 68.76; H, 6.76; N, 5.53.

Found: C, 68.72; H, 6.71; N, 5.58.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.95 (3H, t, J=7.4 Hz), 0.99 (9H, s), 1.41-1.53 (2H, m), 1.75-1.89 (2H, m), 3.86 (3H, s), 3.94-3.95 (4H, m), 3.99 (3H, s), 5.13 (2H, bs), 7.15 (1H, d, J=9.0 Hz), 7.67-7.84 (4H, m), 8.25 (1H, d, J=9.0 Hz).

(8) Tert-butyl (4-butoxy-5,6-dimethoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in

Example 1 (6)).

Elemental analysis for  $\text{C}_{26}\text{H}_{40}\text{N}_2\text{O}_6$

Calculated: C, 65.52; H, 8.46; N, 5.88.

Found: C, 65.17; H, 8.30; N, 5.89.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.98 (9H, s), 0.99 (3H, t, J=7.3 Hz), 1.45 (9H, s), 1.46-1.55 (2H, m), 1.74-1.84 (2H, m), 3.80 (2H, t, J=6.2 Hz), 3.85 (3H, s), 3.99 (3H, s), 4.14 (2H, bs), 4.56 (2H, d, J=5.6 Hz), 4.67 (1H, bs), 7.15 (1H, d, J=9.0 Hz), 8.26 (1H, d, J=9.0 Hz).

(9) 3-(Aminomethyl)-4-butoxy-5,6-dimethoxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1

(7))

Melting point 156-157°C.

Elemental analysis for  $C_{21}H_{33}N_2O_4Cl$

Calculated: C, 61.08; H, 8.05; N, 6.78.

5 Found: C, 60.71; H, 8.05; N, 6.78.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.88 (9H, s), 0.97 (3H, t, J=7.3 Hz),  
1.43-1.54 (2H, m), 1.76-1.83 (2H, m), 3.76 (3H, s), 3.79  
(2H, bs), 3.94 (3H, s), 4.07 (2H, bs), 4.22 (2H, s),  
7.40 (1H, d, J=9.0 Hz), 8.11 (1H, d, J=9.0 Hz), 8.52 (3H,  
10 bs).

#### Example 70

3-(Aminomethyl)-4-butoxy-6,7-dimethoxy-2-neopentyl-  
1(2H)-isoquinolinone hydrochloride

(1) 2-(Ethoxycarbonyl)-4,5-dimethoxybenzoic acid

15 (synthesized according to the method similar to that in  
Example 69 (1))

Melting point 130-131°C.

Elemental analysis for  $C_{12}H_{14}O_6 \cdot 1/4H_2O$

Calculated: C, 55.70; H, 5.65.

20 Found: C, 56.06; H, 5.53.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.39 (3H, t, J=7.2 Hz), 3.98 (6H, s),  
4.40 (2H, q, J=7.2 Hz), 7.22 (1H, s), 7.50 (1H, s), 8.01  
(1H, s).

(2) Ethyl 6,7-dimethoxy-4-hydroxy-2-neopentyl-1-oxo-1,2-  
25 dihydro-3-isoquinolinecarboxylate (synthesized according  
to the method similar to that in Example 69 (2))

Elemental analysis for  $C_{19}H_{25}NO_6$

Calculated: C, 62.80; H, 6.93; N, 3.85.

Found: C, 62.58; H, 6.89; N, 3.82.

30  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.85 (9H, s), 1.47 (3H, t, J=7.2 Hz),  
4.04 (6H, s), 4.47 (2H, q, J=7.2 Hz), 4.55 (2H, bs),  
7.49 (1H, s), 7.85 (1H, s), 11.04 (1H, s).

(3) Ethyl 4-butoxy-6,7-dimethoxy-2-neopentyl-1-oxo-1,2-  
dihydro-3-isoquinolinecarboxylate (synthesized according  
35 to the method similar to that in Example 1 (2))

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.94 (9H, s), 1.02 (3H, t, J=7.3 Hz),



1.44 (3H, t, J=7.3 Hz), 1.49-1.67 (2H, m), 1.74-1.87 (2H, m), 3.96 (2H, t, J=6.4 Hz), 4.01 (3H, s), 4.02 (3H, s), 4.14 (2H, bs), 4.42 (2H, q, J=7.1 Hz), 7.15 (1H, s), 7.83 (1H, s).

- 5 (4) 4-Butoxy-6,7-dimethoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 209-210°C.

- 10 Elemental analysis for  $C_{21}H_{29}NO_6$

Calculated: C, 64.43; H, 7.47; N, 3.58.

Found: C, 64.14; H, 7.34; N, 3.46.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.91 (9H, s), 1.01 (3H, t, J=7.2 Hz), 1.44-1.65 (2H, m), 1.74-1.88 (2H, m), 3.92 (3H, s),

- 15 4.03-4.18 (7H, m), 6.60 (1H, s), 7.31 (1H, s).

(5) 4-Butoxy-6,7-dimethoxy-3-hydroxymethyl-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

Melting point 142-143°C.

- 20 Elemental analysis for  $C_{21}H_{31}NO_5 \cdot 1/4H_2O$

Calculated: C, 66.03; H, 8.31; N, 3.67.

Found: C, 66.32; H, 8.46; N, 3.83.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.95 (9H, s), 1.03 (3H, t, J=7.3 Hz), 1.55-1.67 (2H, m), 1.77-1.87 (2H, m), 3.65 (1H, bs),

- 25 3.80 (2H, t, J=6.2 Hz), 3.95 (3H, s), 4.02 (3H, s), 4.22 (2H, bs), 4.84 (2H, bs), 6.76 (1H, s), 7.57 (1H, s).

(6) 4-Butoxy-3-chloromethyl-6,7-dimethoxy-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

- 30  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.00 (9H, s), 1.05 (3H, t, J=7.3 Hz), 1.58-1.73 (2H, m), 1.82-1.93 (2H, m), 3.97 (2H, t, J=6.4 Hz), 4.02 (6H, s), 4.21 (2H, bs), 4.90 (2H, bs), 7.12 (1H, s), 7.82 (1H, s).

- (7) 2-((4-Butoxy-6,7-dimethoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to
- 35

that in Example 4 (6))

Melting point 210-212°C.

Elemental analysis for  $C_{29}H_{34}N_2O_6$

Calculated: C, 68.76; H, 6.76; N, 5.53.

5 Found: C, 68.61; H, 6.65; N, 5.55.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.01 (3H, t,  $J=7.4$  Hz), 1.02 (9H, s),  
1.49-1.67 (2H, m), 1.82-1.96 (2H, m), 3.99 (3H, s), 4.00  
(3H, s), 4.03 (2H, t,  $J=6.6$  Hz), 4.10 (2H, bs), 5.07 (2H,  
s), 7.13 (1H, s), 7.68-7.83 (5H, m).

10 (8) Tert-butyl (4-butoxy-6,7-dimethoxy-2-neopentyl-1-  
oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate  
(synthesized according to the method similar to that in  
Example 1 (6)).

Melting point 197-198°C.

15 Elemental analysis for  $C_{26}H_{40}N_2O_6 \cdot 1/2H_2O$

Calculated: C, 64.31; H, 8.51; N, 5.77.

Found: C, 64.68; H, 8.43; N, 5.62.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.00 (9H, s), 1.04 (3H, t,  $J=7.2$  Hz),  
1.46 (9H, s), 1.55-1.70 (2H, m), 1.79-1.93 (2H, m), 3.86  
20 (2H, t,  $J=6.4$  Hz), 4.00 (3H, s), 4.05 (3H, s), 4.10 (2H,  
bs), 4.56 (2H, d,  $J=5.4$  Hz), 4.80 (1H, bs), 7.03 (1H, s),  
7.77 (1H, s).

(9) 3-(Aminomethyl)-4-butoxy-6,7-dimethoxy-2-neopentyl-  
1(2H)-isoquinolinone hydrochloride (synthesized  
25 according to the method similar to that in Example 1  
(7)).

Melting point 231-233°C.

Elemental analysis for  $C_{21}H_{33}N_2O_4Cl \cdot H_2O$

Calculated: C, 58.53; H, 8.19; N, 6.50.

30 Found: C, 58.77; H, 8.23; N, 6.61.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.90 (9H, s), 1.00 (3H, t,  $J=7.3$  Hz),  
1.53-1.65 (2H, m), 1.77-1.88 (2H, m), 3.90 (3H, s), 3.94  
(3H, s), 3.95 (2H, t,  $J=7.8$  Hz), 4.09 (2H, bs), 4.22 (2H,  
s), 7.10 (1H, s), 7.65 (1H, s), 8.56 (3H, bs).

35 Example 71

5-(Aminomethyl)-4-butoxy-6-neopentylthieno[2,3-

c]pyridin-7(6H)-one hydrochloride

(1) 3-(Ethoxycarbonyl)-2-thiophenecarboxylic acid  
(synthesized according to the method similar to that in  
Example 69 (1))

5 Melting point 80-81°C.

Elemental analysis for  $C_8H_8O_4S$

Calculated: C, 47.99; H, 4.03.

Found: C, 47.91; H, 3.79.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.46 (3H, t,  $J=7.1$  Hz), 4.50 (2H, q,  
10  $J=7.1$  Hz), 7.57 (1H, d,  $J=5.3$  Hz), 7.63 (1H, d,  $J=5.3$   
Hz).

(2) Ethyl 4-hydroxy-6-neopentyl-7-oxo-6,7-  
dihydrothieno[2,3-c]pyridin-5-carboxylate (synthesized  
according to the method similar to that in Example 69  
15 (2))

Melting point 95.5-97°C.

Elemental analysis for  $C_{15}H_{19}NO_4S$

Calculated: C, 58.23; H, 6.19; N, 4.53.

Found: C, 58.12; H, 6.01; N, 4.48.

20  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.85 (9H, s), 1.46 (3H, t,  $J=7.2$  Hz),  
4.47 (2H, q,  $J=7.2$  Hz), 4.53 (2H, bs), 7.55 (1H, d,  
 $J=5.1$  Hz), 7.72 (1H, d,  $J=5.1$  Hz), 10.66 (1H, s).

(3) Ethyl 4-butoxy-6-neopentyl-7-oxo-6,7-  
dihydrothieno[2,3-c]pyridine-5-carboxylate (synthesized  
25 according to the method similar to that in Example 1  
(2).)

Melting point 74-74.5°C.

Elemental analysis for  $C_{19}H_{27}NO_4S$

Calculated: C, 62.44; H, 7.45; N, 3.83.

30 Found: C, 62.48; H, 7.70; N, 3.89.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.94 (9H, s), 0.99 (3H, t,  $J=7.3$  Hz),  
1.43 (3H, t,  $J=7.2$  Hz), 1.49-1.60 (2H, m), 1.70-1.84 (2H,  
m), 4.00 (2H, t,  $J=6.6$  Hz), 4.14 (2H, bs), 4.41 (2H, q,  
 $J=7.2$  Hz), 7.32 (1H, d,  $J=5.2$  Hz), 7.72 (1H, d,  $J=5.2$  Hz).

35 (4) 4-Butoxy-6-neopentyl-7-oxo-6,7-dihydrothieno[2,3-  
c]pyridine-5-carboxylic acid (synthesized according to

the method similar to that in Example 4 (3))

Melting point 111-112°C.

Elemental analysis for  $C_{17}H_{23}NO_4S$

Calculated: C, 60.51; H, 6.87; N, 4.15.

5 Found: C, 60.53; H, 6.87; N, 4.29.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.95 (9H, s), 0.98 (3H, t,  $J=7.4$  Hz),  
1.43-1.61 (2H, m), 1.74-1.84 (2H, m), 4.08 (2H, t,  $J=6.4$   
Hz), 4.31 (2H, bs), 5.98 (1H, bs), 7.34 (1H, d,  $J=5.2$   
Hz), 7.75 (1H, d,  $J=5.2$  Hz).

10 (5) 4-Butoxy-5-hydroxymethyl-6-neopentylthieno[2,3-  
c]pyridin-7(6H)-one (synthesized according to the method  
similar to that in Example 4 (4))

Melting point 110-111°C.

Elemental analysis for  $C_{17}H_{25}NO_3S$

15 Calculated: C, 63.13; H, 7.79; N, 4.33.

Found: C, 63.11; H, 7.59; N, 4.44.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.97 (9H, s), 1.02 (3H, t,  $J=7.4$  Hz),  
1.47-1.68 (2H, m), 1.76-1.89 (2H, m), 3.98 (2H, t,  $J=6.6$   
Hz), 4.22 (2H, bs), 4.86 (2H, bs), 7.24 (1H, d,  $J=5.4$   
20 Hz), 7.62 (1H, d,  $J=5.4$  Hz).

(6) 4-Butoxy-5-chloromethyl-6-neopentylthieno[2,3-  
c]pyridin-7(6H)-one (synthesized according to the method  
similar to that in Example 4 (5))

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.01 (9H, s), 1.02 (3H, t,  $J=7.3$  Hz),  
25 1.52-1.63 (2H, m), 1.78-1.88 (2H, m), 4.01 (2H, t,  $J=6.4$   
Hz), 4.20 (2H, bs), 4.89 (2H, bs), 7.30 (1H, d,  $J=5.2$   
Hz), 7.69 (1H, d,  $J=5.2$  Hz).

(7) 2-((4-Butoxy-6-neopentyl-7-oxo-6,7-  
dihydrothieno[2,3-c]pyridin-5-yl)methyl)-1H-isoindole-  
30 1,3(2H)-dione (synthesized according to the method  
similar to that in Example 4 (6))

Melting point 118-119°C.

Elemental analysis for  $C_{25}H_{28}N_2O_4S$

Calculated: C, 66.35; H, 6.24; N, 6.19.

35 Found: C, 66.26; H, 6.17; N, 6.27.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (3H, t,  $J=7.2$  Hz), 1.03 (9H, s),

1.41-1.60 (2H, m), 1.76-1.91 (2H, m), 4.08 (2H, t, J=6.8 Hz), 4.14 (2H, bs), 5.08 (2H, s), 7.30 (1H, d, J=5.0 Hz), 7.67 (1H, d, J=5.0 Hz), 7.69-7.84 (4H, m).

(8) Tert-butyl (4-butoxy-6-neopentyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridin-5-yl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

Melting point 131-131.5°C.

Elemental analysis for  $C_{22}H_{34}N_2O_4S$

10 Calculated: C, 62.53; H, 8.11; N, 6.63.

Found: C, 62.47; H, 8.13; N, 6.63.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.01 (9H, s), 1.02 (3H, t, J=7.1 Hz), 1.44 (9H, s), 1.46-1.68 (2H, m), 1.75-1.89 (2H, m), 3.93 (2H, t, J=6.4 Hz), 4.17 (2H, bs), 4.56 (2H, d, J=5.2 Hz), 15 4.70 (1H, bs), 7.27 (1H, d, J=5.5 Hz), 7.68 (1H, d, J=5.5 Hz).

(9) 5-(Aminomethyl)-4-butoxy-6-neopentylthieno[2,3-c]pyridin-7(6H)-one hydrochloride (synthesized according to the method similar to that in Example 1 (7))

20 Elemental analysis for  $C_{17}H_{27}N_2O_2ClS \cdot 1/4H_2O$

Calculated: C, 56.18; H, 7.63; N, 7.71.

Found: C, 56.01; H, 7.64; N, 7.67.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.91 (9H, s), 0.97 (3H, t, J=7.4 Hz), 1.45-1.56 (2H, m), 1.73-1.83 (2H, m), 4.01 (2H, t, J=6.2 Hz), 25 4.13 (2H, bs), 4.23 (2H, bs), 7.47 (1H, d, J=5.1 Hz), 8.16 (1H, d, J=5.1 Hz), 8.53 (3H, bs).

#### Example 72

6-(Aminomethyl)-7-butoxy-5-neopentylthieno[3,2-c]pyridin-4(5H)-one hydrochloride

30 (1) 2-(Ethoxycarbonyl)-3-thiophenecarboxylic acid (synthesized according to the method similar to that in Example 69 (1))

Melting point 94-95°C.

Elemental analysis for  $C_8H_8O_4S$

35 Calculated: C, 47.99; H, 4.03.

Found: C, 47.91; H, 3.79.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 1.28 (3H, t,  $J=7.0$  Hz), 4.28 (2H, q,  $J=7.0$  Hz), 7.32 (1H, d,  $J=5.1$  Hz), 7.89 (1H, d,  $J=5.1$  Hz).

(2) Ethyl 7-hydroxy-5-neopentyl-4-oxo-4,5-

- 5 dihydrothieno[3,2-c]pyridine-6-carboxylate (synthesized according to the method similar to that in Example 69 (2)).

Melting point 110-111°C.

Elemental analysis for  $\text{C}_{15}\text{H}_{19}\text{NO}_4\text{S}$ .

- 10 Calculated: C, 58.23; H, 6.19; N, 4.53.

Found: C, 58.28; H, 6.19; N, 4.50.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.86 (9H, s), 1.47 (3H, t,  $J=7.2$  Hz), 4.48 (2H, q,  $J=7.2$  Hz), 7.58 (1H, d,  $J=5.2$  Hz), 7.72 (1H, d,  $J=5.2$  Hz), 10.62 (1H, s).

- 15 (3) Ethyl 7-butoxy-5-neopentyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-6-carboxylate (synthesized according to the method similar to that in Example 1 (2)).

- 20  $^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.94 (9H, s), 0.99 (3H, t,  $J=7.5$  Hz), 1.43 (3H, t,  $J=7.2$  Hz), 1.43-1.61 (2H, m), 1.70-1.84 (2H, m), 4.07 (2H, t,  $J=6.6$  Hz), 4.14 (2H, bs), 4.41 (2H, q,  $J=7.2$  Hz), 7.41 (1H, d,  $J=5.3$  Hz), 7.68 (1H, d,  $J=5.3$  Hz).

- (4) 7-Butoxy-5-neopentyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-6-carboxylic acid (synthesized according to the method similar to that in Example 4 (3)).

- 25 Melting point 137-138°C.

Elemental analysis for  $\text{C}_{17}\text{H}_{23}\text{NO}_4\text{S}$ .

Calculated: C, 60.51; H, 6.87; N, 4.15.

Found: C, 60.66; H, 6.86; N, 4.10.

- 30  $^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.93 (9H, s), 0.98 (3H, t,  $J=7.4$  Hz), 1.43-1.61 (2H, m), 1.72-1.86 (2H, m), 4.14 (2H, t,  $J=6.4$  Hz), 4.21 (2H, bs), 6.83 (1H, bs), 7.44 (1H, d,  $J=5.3$  Hz), 7.68 (1H, d,  $J=5.3$  Hz).

- (5) 7-Butoxy-6-hydroxymethyl-5-neopentylthieno[3,2-c]pyridin-4(5H)-one (synthesized according to the method similar to that in Example 4 (4)).

Melting point 102-103°C.

Elemental analysis for  $C_{17}H_{25}NO_3S \cdot 1/2H_2O$

Calculated: C, 61.42; H, 7.88; N, 4.21.

Found: C, 61.39; H, 7.61; N, 4.36.

- 5  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.95 (9H, s), 1.02 (3H, t, J=7.2 Hz), 1.47-1.66 (2H, m), 1.75-1.89 (2H, m), 3.10 (1H, bs), 4.04 (2H, t, J=6.5 Hz), 4.15 (2H, bs), 4.83 (2H, bs), 7.22-7.26 (1H, m), 7.52-7.56 (1H, m).

- 10 (6) 7-Butoxy-6-chloromethyl-5-neopentylthieno[3,2-c]pyridin-4(5H)-one (synthesized according to the method similar to that in Example 4 (5))

- $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.01 (9H, s), 1.02 (3H, t, J=7.3 Hz), 1.52-1.63 (2H, m), 1.77-1.88 (2H, m), 4.08 (2H, t, J=6.4 Hz), 4.14 (2H, bs), 4.87 (2H, bs), 7.35 (1H, d, J=5.5 Hz), 7.68 (1H, d, J=5.5 Hz).

- (7) 2-((7-Butoxy-5-neopentyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridin-6-yl)methyl)-1H-isoindole-1,3(2H)-dione (synthesized according to the method similar to that in Example 4 (6))

- 20 Melting point 136-137°C.

Elemental analysis for  $C_{25}H_{28}N_2O_4S$

Calculated: C, 66.35; H, 6.24; N, 6.19.

Found: C, 66.27; H, 6.14; N, 6.22.

- 25  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (3H, t, J=7.2 Hz), 1.02 (9H, s), 1.45-1.60 (2H, m), 1.76-1.90 (2H, m), 4.14 (2H, bs), 4.16 (2H, t, J=6.6 Hz), 5.07 (2H, s), 7.29 (1H, d, J=5.2 Hz), 7.64 (1H, d, J=5.2 Hz), 7.69-7.83 (4H, m).

- (8) Tert-butyl (7-butoxy-5-neopentyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridin-6-yl)methylcarbamate  
30 (synthesized according to the method similar to that in Example 1 (6))

Melting point 141-142°C.

Elemental analysis for  $C_{22}H_{34}N_2O_4S$

Calculated: C, 62.53; H, 8.11; N, 6.63.

- 35 Found: C, 62.50; H, 8.08; N, 6.66.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.01 (9H, s), 1.02 (3H, t, J=7.1 Hz),

1.44 (9H, s), 1.49-1.64 (2H, m), 1.74-1.88 (2H, m), 4.00 (2H, t, J=6.4 Hz), 4.14 (2H, bs), 4.56 (2H, d, J=5.0 Hz), 4.70 (1H, bs), 7.29 (1H, d, J=5.1 Hz), 7.64 (1H, d, J=5.1 Hz).

- 5 (9) 6-(Aminomethyl)-7-butoxy-5-neopentylthieno[3,2-c]pyridin-4(5H)-one hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 204-206°C.

Elemental analysis for  $C_{17}H_{27}N_2O_2ClS$ :

- 10 Calculated: C, 56.89; H, 7.58; N, 7.80.

Found: C, 56.98; H, 7.46; N, 7.61.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.91 (9H, s), 0.98 (3H, t, J=7.4 Hz),

1.44-1.59 (2H, m), 1.71-1.92 (2H, m), 4.07 (2H, t, J=6.4 Hz), 4.09 (2H, bs), 4.24 (2H, d, J=5.3 Hz), 7.56 (1H, d,

- 15 J=5.3 Hz), 7.77 (1H, d, J=5.3 Hz), 8.58 (3H, bs).

#### Example 74

3-(Aminomethyl)-6-bromo-4-butoxy-2-isobutyl-1(2H)-isoquinolinone hydrochloride

(1) Ethyl 6-bromo-4-hydroxy-2-isobutyl-1-oxo-1,2-

- 20 dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (1))

Melting point 74-75°C.

Elemental analysis for  $C_{16}H_{18}NO_4Br$

Calculated: C, 52.19; H, 4.93; N, 3.80.

- 25 Found: C, 52.15; H, 4.89; N, 3.85.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.82 (6H, d, J=6.6 Hz), 1.46 (3H, t, J=7.2 Hz), 1.78-1.88 (1H, m), 4.39 (2H, d, J=5.6 Hz),

4.49 (2H, q, J=7.2 Hz), 7.78 (1H, dd, J=2.0, 8.4 Hz),

8.30 (1H, d, J=2.0 Hz), 8.31 (1H, d, J=8.4 Hz), 11.14

- 30 (1H, s).

(2) Ethyl 6-bromo-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))

Melting point 88-89°C.

- 35 Elemental analysis for  $C_{20}H_{26}NO_4Br$

Calculated: C, 56.61; H, 6.18; N, 3.30.



Found: C, 56.64; H, 6.13; N, 3.38.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.90 (6H, d,  $J=7.0$  Hz), 1.01 (3H, t,  $J=7.4$  Hz), 1.44 (3H, t,  $J=7.2$  Hz), 1.48-1.63 (2H, m), 1.72-1.83 (2H, m), 2.05-2.19 (1H, m), 3.88 (2H, d,  $J=7.4$  Hz), 3.95 (2H, t,  $J=6.4$  Hz), 4.46 (2H, q,  $J=7.2$  Hz), 7.65 (1H, dd,  $J=2.0, 8.6$  Hz), 7.88 (1H, d,  $J=2.0$  Hz), 8.29 (1H, d,  $J=8.6$  Hz).

(3) 6-Bromo-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 177-178°C.

Elemental analysis for  $\text{C}_{18}\text{H}_{22}\text{NO}_4\text{Br}$

Calculated: C, 54.56; H, 5.60; N, 3.53.

Found: C, 54.57; H, 5.63; N, 3.57.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.90 (6H, d,  $J=6.6$  Hz), 1.00 (3H, t,  $J=7.4$  Hz), 1.45-1.63 (2H, m), 1.75-1.89 (2H, m), 2.07-2.23 (1H, m), 4.01 (2H, t,  $J=6.4$  Hz), 4.02 (2H, d,  $J=8.6$  Hz), 6.81 (1H, bs), 7.65 (1H, dd,  $J=1.8, 8.6$  Hz), 7.81 (1H, d,  $J=1.8$  Hz), 8.23 (1H, d,  $J=8.6$  Hz).

(4) 6-Bromo-4-butoxy-3-hydroxymethyl-2-isobutyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (4))

Melting point 92-93°C.

Elemental analysis for  $\text{C}_{18}\text{H}_{24}\text{NO}_3\text{Br} \cdot 1/2\text{H}_2\text{O}$

Calculated: C, 55.25; H, 6.43; N, 3.58.

Found: C, 55.62; H, 6.35; N, 3.75.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.93 (6H, d,  $J=6.6$  Hz), 1.04 (3H, t,  $J=7.4$  Hz), 1.50-1.68 (2H, m), 1.79-1.93 (2H, m), 2.11-2.28 (1H, m), 2.47 (1H, bs), 3.88 (2H, t,  $J=6.4$  Hz), 4.08 (2H, d,  $J=7.8$  Hz), 4.80 (2H, s), 7.55 (1H, d,  $J=8.6$  Hz), 7.80 (1H, s), 8.18 (1H, d,  $J=8.6$  Hz).

(5) 6-Bromo-4-butoxy-3-chloromethyl-2-isobutyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 4 (5))

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.95 (6H, d,  $J=7.0$  Hz), 1.05 (3H, t,  $J=7.2$  Hz), 1.52-1.75 (2H, m), 1.86-1.96 (2H, m), 2.04-

2.23 (1H, m), 3.98 (2H, t, J=6.4 Hz), 4.07 (2H, d, J=7.4 Hz), 4.80 (2H, s), 7.63 (1H, dd, J=2.0, 8.4 Hz), 7.88 (1H, d, J=2.0 Hz), 8.29 (1H, d, J=8.4 Hz).

(6) 2-((6-Bromo-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl)-1H-isoindole-1,3(2H)-dione  
(synthesized according to the method similar to that in Example 4 (6))

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.96 (6H, d, J=7.0 Hz), 1.00 (3H, t, J=7.3 Hz), 1.44-1.58 (2H, m), 1.79-1.95 (2H, m), 2.08-2.22 (1H, m), 3.95-4.05 (4H, m), 5.02 (2H, s), 7.59 (1H, dd, J=2.0, 8.8 Hz), 7.71-7.90 (5H, m), 8.27 (1H, d, J=8.8 Hz).

(7) Tert-butyl (6-bromo-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 1 (6))

Melting point 138-139°C.

Elemental analysis for C<sub>23</sub>H<sub>33</sub>N<sub>2</sub>O<sub>4</sub>Br

Calculated: C, 57.38; H, 6.91; N, 5.82.

Found: C, 57.41; H, 6.79; N, 5.76.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.95 (6H, d, J=6.6 Hz), 1.04 (3H, t, J=7.3 Hz), 1.46 (9H, s), 1.53-1.67 (2H, m), 1.80-1.93 (2H, m), 2.05-2.23 (1H, m), 3.85 (2H, t, J=6.6 Hz), 3.98 (2H, d, J=7.6 Hz), 4.41 (2H, d, J=5.4 Hz), 4.73 (1H, bs), 7.59 (1H, dd, J=2.0, 8.6 Hz), 7.82 (1H, d, J=2.0 Hz), 8.26 (1H, d, J=8.6 Hz).

(8) 3-(Aminomethyl)-6-bromo-4-butoxy-2-isobutyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 133-134°C.

Elemental analysis for C<sub>18</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>BrCl 1/2H<sub>2</sub>O

Calculated: C, 50.66; H, 6.38; N, 6.56.

Found: C, 51.05; H, 6.56; N, 6.68.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.88 (6H, d, J=7.0 Hz), 1.00 (3H, t, J=7.4 Hz), 1.46-1.65 (2H, m), 1.76-1.91 (2H, m), 1.96-2.10 (1H, m), 3.93 (2H, t, J=6.4 Hz), 3.96 (2H, d, J=7.6

Hz), 4.18 (2H, d, J=4.4 Hz), 7.79 (1H, dd, J=2.0, 8.6 Hz), 7.87 (1H, d, J=2.0 Hz), 8.20 (1H, d, J=8.6 Hz), 8.69 (3H, bs).

#### Example 75

- 5 Methyl 3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylate hydrochloride  
(1) A mixture of tert-butyl (6-bromo-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to  
10 the method similar to that in Example 74 (7)) (2.41 g, 5 mmol), 1,3-bis(diphenylphosphino)propane (0.21 g, 0.5 mmol) and triethylamine (0.77 ml, 5.5 mmol) in dimethyl sulfoxide (30 ml) and methanol (20 ml) was stirred under a carbon monoxide atmosphere at room temperature for 10  
15 min. To the obtained mixture was added palladium acetate (0.11 g, 0.5 mmol) and the mixture was stirred with heating under a carbon monoxide atmosphere at 60°C for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the  
20 extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give methyl 4-butoxy-3-((tert-butoxycarbonyl)amino)methyl-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylate (1.92 g, 83.5%) as  
25 crystals.

Melting point 148-149°C.

Elemental analysis for  $C_{25}H_{36}N_2O_6$ .

Calculated: C, 65.20; H, 7.88; N, 6.08.

- 30 Found: C, 65.30; H, 7.67; N, 6.17.

- $^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.97 (6H, d, J=6.8 Hz), 1.05 (3H, t, J=7.3 Hz), 1.47 (9H, s), 1.56-1.71 (2H, m), 1.83-1.93 (2H, m), 2.05-2.25 (1H, m), 3.89 (2H, t, J=6.6 Hz), 3.99 (3H, s), 4.01 (2H, d, J=7.6 Hz), 4.53 (2H, d, J=5.4 Hz),  
35 4.77 (1H, bs), 8.09 (1H, dd, J=1.9, 8.4 Hz), 8.40 (1H, d, J=1.9 Hz), 8.47 (1H, d, J=8.4 Hz).

(2) Methyl 3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylate hydrochloride (synthesized according to the method similar to that in Example 1 (7))

5 Melting point 135-136°C.

Elemental analysis for  $C_{20}H_{29}N_2O_4Cl$

Calculated: C, 60.52; H, 7.36; N, 7.06.

Found: C, 60.20; H, 7.48; N, 7.02.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.89 (6H, d,  $J=6.6$  Hz), 1.02 (3H, t,  $J=7.3$  Hz), 1.51-1.70 (2H, m), 1.80-1.92 (2H, m), 1.99-2.11 (1H, m), 3.95-4.01 (7H, m), 4.21 (2H, s), 8.11 (1H, dd,  $J=1.4$ , 8.2 Hz), 8.35 (1H, d,  $J=1.4$  Hz), 8.41 (1H, d,  $J=8.2$  Hz), 8.70 (3H, bs).

#### Example 76

15 3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid hydrochloride

(1) To a solution of methyl 4-butoxy-3-(((tert-butoxycarbonyl)amino)methyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 75 (1)) (1.61 g, 3.5 mmol) in tetrahydrofuran (10 ml) and methanol (10 ml) was added 1N sodium hydroxide (5 ml). The obtained mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diethyl ether to give 4-butoxy-3-(((tert-butoxycarbonyl)amino)methyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid (1.54 g, 98.7%) as crystals.

Melting point 185-186°C.

Elemental analysis for  $C_{24}H_{34}N_2O_6$

35 Calculated: C, 64.55; H, 7.67; N, 6.27.

Found: C, 64.77; H, 7.40; N, 6.10.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.96 (6H, d, J=6.6 Hz), 1.07 (3H, t, J=7.4 Hz), 1.49 (9H, s), 1.50-1.72 (2H, m), 1.84-1.98 (2H, m), 2.14-2.21 (1H, m), 3.90 (2H, t, J=6.4 Hz), 4.00 (2H, d, J=6.8 Hz), 4.55 (2H, d, J=5.0 Hz), 5.37 (1H, bs),  
 5 8.08-8.13 (1H, m), 8.35-8.46 (2H, m).

(2) 3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic hydrochloride  
 (synthesized according to the method similar to that in Example 1 (7))

10 Melting point 238-239°C.

Elemental analysis for C<sub>19</sub>H<sub>27</sub>N<sub>2</sub>O<sub>4</sub>Cl

Calculated: C, 59.60; H, 7.11; N, 7.32.

Found: C, 59.42; H, 7.04; N, 7.18.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.89 (6H, d, J=6.6 Hz), 1.01 (3H, t, J=7.4 Hz), 1.50-1.69 (2H, m), 1.80-1.93 (2H, m), 1.99-2.12 (1H, m), 3.97 (2H, t, J=6.4 Hz), 3.99 (2H, d, J=7.6 Hz), 4.21 (2H, s), 8.09 (1H, dd, J=1.4, 8.4 Hz), 8.34 (1H, d, J=1.4 Hz), 8.38 (1H, d, J=8.4 Hz), 8.69 (3H, bs).

#### Example 77

20 3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide hydrochloride

(1) A solution of 4-butoxy-3-((tert-butoxycarbonyl)amino)methyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid (Example 76 (1))

25 (0.45 g, 3.5 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.38 g, 2 mmol) and 1-hydroxybenzotriazole ammonium salt (0.30 g, 2 mmol) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 3 h. The reaction mixture was

30 poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl ((6-aminocarbonyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.35 g, 79.5%) as

crystals.

Melting point 159-160°C.

Elemental analysis for  $C_{24}H_{35}N_3O_5$

Calculated: C, 64.70; H, 7.92; N, 9.43.

5 Found: C, 64.53; H, 8.01; N, 9.53.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.96 (6H, d,  $J=7.0$  Hz), 1.03 (3H, t,  $J=7.3$  Hz), 1.48 (9H, s), 1.49-1.63 (2H, m), 1.80-1.95 (2H, m), 2.10-2.21 (1H, m), 3.87 (2H, t,  $J=6.4$  Hz), 4.00 (2H, d,  $J=7.2$  Hz), 4.52 (2H, d,  $J=5.6$  Hz), 5.07 (1H, bs),  
10 5.99 (1H, bs), 6.48 (1H, bs), 7.75 (1H, d,  $J=8.0$  Hz), 8.10 (1H, s), 8.35 (1H, d,  $J=8.0$  Hz).

(2) 3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide hydrochloride  
(synthesized according to the method similar to that in

15 Example 1 (7))

Melting point 171-173°C.

Elemental analysis for  $C_{19}H_{28}N_3O_3Cl \cdot H_2O$

Calculated: C, 57.06; H, 7.56; N, 10.51.

Found: C, 57.41; H, 7.62; N, 10.59.

20  $^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.89 (6H, d,  $J=7.0$  Hz), 1.01 (3H, t,  $J=7.3$  Hz), 1.48-1.66 (2H, m), 1.80-2.07 (3H, m), 3.94-4.00 (4H, m), 4.20 (2H, s), 7.70 (1H, s), 8.04 (1H, dd,  $J=1.6, 8.4$  Hz), 8.22 (1H, d,  $J=1.6$  Hz), 8.33 (1H, d,  $J=8.4$  Hz), 8.35 (1H, s), 8.60 (3H, bs).

25 Example 78

3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarbonitrile hydrochloride

(1) A solution of tert-butyl {(6-aminocarbonyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-

30 isoquinolinyl}methylcarbamate (Example 77 (1)) (0.54 g, 1.2 mmol) and cyanuric chloride (0.66 g, 3.6 mmol) in N,N-dimethylformamide (10 mmol) was stirred at 0°C for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed  
35 with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was

recrystallized from ethyl acetate - n-hexane to give tert-butyl (4-butoxy-6-cyano-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.41 g, 80.4%) as crystals.

<sup>5</sup> Melting point 126-127°C.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.97 (6H, d, J=6.6 Hz), 1.05 (3H, t, J=7.3 Hz), 1.47 (9H, s), 1.48-1.67 (2H, m), 1.82-1.96 (2H, m), 2.11-2.25 (1H, m), 3.86 (2H, t, J=6.4 Hz), 4.02 (2H, d, J=7.0 Hz), 4.53 (2H, d, J=5.2 Hz), 4.73 (1H, bs),  
<sup>10</sup> 7.68 (1H, d, J=8.0 Hz), 8.01 (1H, s), 8.50 (1H, d, J=8.0 Hz).

(2) 3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarbonitrile hydrochloride (synthesized according to the method similar to that in

<sup>15</sup> Example 1 (7))

Melting point 135-136°C.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.89 (6H, d, J=6.6 Hz), 1.00 (3H, t, J=7.2 Hz), 1.41-1.64 (2H, m), 1.81-1.91 (2H, m), 1.99-2.08 (1H, m), 3.93-4.02 (4H, m), 4.20 (2H, s), 7.99 (1H,  
<sup>20</sup> d, J=8.2 Hz), 8.24 (1H, s), 8.42 (1H, d, J=8.2 Hz), 8.74 (3H, bs).

#### Example 79

3-(Aminomethyl)-4-butoxy-6-hydroxymethyl-2-isobutyl-1(2H)-isoquinoline hydrochloride

<sup>25</sup> (1) To a solution of 4-butoxy-3-((tert-butoxycarbonyl)-amino)methyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 76 (1)) (0.45 g, 3.5 mmol) and N-methylmorpholine (0.13 ml, 1.2 mmol) in  
<sup>30</sup> tetrahydrofuran (10 ml) was added ethyl chloroformate (0.12 ml, 1.2 mmol) at 0°C, and the mixture was stirred at 0°C for 10 min. To the obtained mixture was added sodium tetrahydroborate (0.11 g, 3 mmol) and the mixture was stirred at 0°C for 1 h. The reaction mixture was  
<sup>35</sup> poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous

magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl (4-butoxy-6-hydroxymethyl-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.33 g, 76.7%) as crystals.

Melting point 153-154°C.

Elemental analysis for  $C_{24}H_{36}N_2O_5$

Calculated: C, 66.64; H, 8.39; N, 6.48.

10 Found: C, 66.61; H, 8.21; N, 6.44.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.95 (6H, d,  $J=6.6$  Hz), 1.01 (3H, t,  $J=7.4$  Hz), 1.40-1.57 (11H, m), 1.78-1.92 (2H, m), 2.11-2.24 (1H, m), 3.80 (2H, t,  $J=6.8$  Hz), 3.97 (2H, d,  $J=7.8$  Hz), 4.50 (2H, d,  $J=5.4$  Hz), 4.82 (2H, s), 5.25 (1H, bs), 7.39-7.51 (2H, m), 8.17-8.21 (1H, m).

(2) 3-(Aminomethyl)-4-butoxy-6-hydroxymethyl-2-isobutyl-1(2H)-isoquinoline hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Elemental analysis for  $C_{19}H_{29}N_2O_3Cl \cdot 1/2H_2O$

20 Calculated: C, 60.39; H, 8.00; N, 7.41.

Found: C, 60.00; H, 7.07; N, 7.07.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.87 (6H, d,  $J=6.4$  Hz), 1.00 (3H, t,  $J=7.1$  Hz), 1.51-1.62 (2H, m), 1.82-2.02 (3H, m), 3.91-3.99 (4H, m), 4.69 (2H, d,  $J=5.2$  Hz), 5.30 (2H, s), 5.53 (1H, bs), 7.52-7.62 (1H, m), 7.74 (1H, s), 8.21-8.30 (1H, m), 8.64 (3H, bs).

#### Example 80

N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl}-N'-methylurea hydrochloride

30 (1) A solution of 4-butoxy-3-((tert-butoxycarbonyl)amino)methyl-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 76 (1)) (0.45 g, 1 mmol), diphenylphosphoryl azide (0.26 ml, 1.2 mmol) and triethylamine (0.17 ml, 1.2 mmol) in N,N-dimethylformamide (10 ml) was stirred at room



temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in toluene (20 ml) and the mixture was refluxed with stirring for 1 h. To the obtained mixture was added a solution of 2N methylamine in tetrahydrofuran (1 ml, 2 mmol), and the mixture was refluxed with stirring for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from tetrahydrofuran - diisopropyl ether to give tert-butyl {4-butoxy-2-isobutyl-6-((methylamino)carbonyl)-amino}-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.39 g, 83.0%) as an amorphous.

Elemental analysis for  $C_{25}H_{38}N_4O_5$

Calculated: C, 63.27; H, 8.07; N, 11.81.

Found: C, 62.96; H, 8.35; N, 11.55.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.93 (6H, d,  $J=5.8$  Hz), 0.95 (3H, t,  $J=6.6$  Hz), 1.45-1.54 (11H, m), 1.64-1.82 (2H, m), 2.05-2.17 (1H, m), 2.86 (3H, d,  $J=4.4$  Hz), 3.83 (2H, t,  $J=6.5$  Hz), 3.98 (2H, d,  $J=7.4$  Hz), 4.50 (2H, d,  $J=5.2$  Hz), 5.02 (1H, bs), 5.98 (1H, bs), 6.99-7.04 (2H, m), 8.06-8.10 (1H, m), 8.39 (1H, s).

(2) N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl}-N'-methylurea hydrochloride (synthesized according to the method similar to that in

Example 1 (7))

Melting point 181-183°C.

Elemental analysis for  $C_{20}H_{31}N_4O_3Cl \cdot 1/2H_2O$

Calculated: C, 57.20; H, 7.68; N, 13.34.

Found: C, 57.13; H, 7.66; N, 13.40.

$^1\text{H-NMR}(\text{DMSO}-d_6)$   $\delta$ : 0.87 (6H, d,  $J=6.6$  Hz), 0.99 (3H, t,  $J=7.1$  Hz), 1.46-1.65 (2H, m), 1.78-2.07 (3H, m), 3.87-

3.93 (4H, m), 4.14 (2H, d, J=4.6 Hz), 6.74 (1H, bs),  
7.48 (1H, dd, J=2.0, 8.8 Hz), 8.04 (1H, d, J=2.0 Hz),  
8.10 (1H, d, J=8.8 Hz), 8.53 (3H, bs), 9.60 (1H, s).

#### Example 81

- 5 Methyl 3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-  
dihydro-6-isoquinolinylcarbamate hydrochloride

(1) Methyl 4-butoxy-3-(((tert-butoxycarbonyl)amino)-  
methyl)-2-isobutyl-1-oxo-1,2-dihydro-6-  
isoquinolinylcarbamate (synthesized according to the  
10 method similar to that in Example 80 (1)).

Elemental analysis for  $C_{25}H_{38}N_4O_5$

Calculated: C, 63.14; H, 7.84; N, 8.84.

Found: C, 62.99; H, 7.87; N, 9.01.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.95 (6H, d, J=7.0 Hz), 1.03 (3H, t,  
15 J=7.1 Hz), 1.46 (9H, s), 1.52-1.67 (2H, m), 1.81-1.95  
(2H, m), 2.09-2.23 (1H, m), 3.82 (3H, s), 3.88 (2H, t,  
J=6.6 Hz), 3.98 (2H, d, J=7.4 Hz), 4.51 (2H, d, J=5.4  
Hz), 4.80 (1H, bs), 7.09 (1H, bs), 7.36 (1H, dd, J=2.0,  
8.8 Hz), 7.89 (1H, d, J=2.0 Hz), 8.33 (1H, d, J=8.8 Hz).

- 20 (2) Methyl 3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-  
1,2-dihydro-6-isoquinolinylcarbamate hydrochloride  
(synthesized according to the method similar to that in  
Example 1 (7)).

Melting point 166-168°C.

- 25 Elemental analysis for  $C_{20}H_{30}N_3O_4Cl \cdot 1/4H_2O$

Calculated: C, 57.69; H, 7.38; N, 10.09.

Found: C, 57.59; H, 7.66; N, 10.02.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.87 (6H, d, J=6.6 Hz), 1.00 (3H, t,  
J=7.4 Hz), 1.47-1.65 (2H, m), 1.79-2.04 (3H, m), 3.73  
30 (3H, s), 3.89-3.94 (4H, m), 4.15 (2H, d, J=4.6 Hz), 7.63  
(1H, dd, J=1.8, 8.8 Hz), 8.03 (1H, d, J=1.8 Hz), 8.17  
(1H, d, J=8.8 Hz), 8.62 (3H, bs), 10.28 (1H, s).

#### Example 82

- 6-Amino-3-(aminomethyl)-4-butoxy-2-isobutyl-1(2H)-  
35 isoquinolinone dihydrochloride

(1) A solution of 4-butoxy-3-(((tert-

butoxycarbonyl)amino)methyl}-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 76 (1)) (0.45 g, 1 mmol), diphenylphosphoryl azide (0.26 ml, 1.2 mmol) and triethylamine (0.17 ml, 1.2 mmol) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in toluene (20 ml) and the mixture was refluxed with stirring for 1 h. To the obtained mixture was added 9H-fluorenylmethanol (0.29 g, 1.5 mmol) and the mixture was refluxed with stirring for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography and recrystallized from tetrahydrofuran - diisopropyl ether to give 9H-fluoren-9-ylmethyl 4-butoxy-3-((tert-butoxycarbonyl)amino)methyl}-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinylcarbamate (0.53 g, 82.8%) as crystals.

Melting point 137-138°C.

Elemental analysis for  $C_{36}H_{45}N_3O_6$ .

Calculated: C, 71.34; H, 7.09; N, 6.57.

Found: C, 71.09; H, 7.03; N, 6.63.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.95 (6H, d,  $J=7.0$  Hz), 1.01 (3H, t,  $J=7.4$  Hz), 1.46 (9H, s), 1.47-1.61 (2H, m), 1.79-1.90 (2H, m), 2.09-2.23 (1H, m), 3.85 (2H, t,  $J=6.4$  Hz), 3.97 (2H, d,  $J=7.4$  Hz), 4.28 (1H, t,  $J=6.2$  Hz), 4.50 (2H, d,  $J=5.2$  Hz), 4.61 (2H, d,  $J=6.2$  Hz), 4.80 (2H, bs), 7.11-7.16 (1H, m), 7.29-7.46 (4H, m), 7.63 (2H, d,  $J=7.0$  Hz), 7.79 (2H, d,  $J=7.0$  Hz), 7.87 (1H, d,  $J=1.8$  Hz), 8.32 (1H, d,  $J=8.8$  Hz).

(2) To a solution of 9H-fluoren-9-ylmethyl 4-butoxy-3-  
{{(tert-butoxycarbonyl)amino}methyl}-2-isobutyl-1-oxo-  
1,2-dihydro-6-isoquinolinylcarbamate (0.45 g, 0.7 mmol)  
in N,N-dimethylformamide (10 ml) was added pyrrolidine  
5 (0.5 ml) and the mixture was stirred at room temperature  
for 1 h. The reaction mixture was poured into water and  
extracted with ethyl acetate. The extract was washed  
with brine, dried over anhydrous magnesium sulfate and  
concentrated under reduced pressure. The residue was  
10 purified by silica gel column chromatography to give  
tert-butyl (6-amino-4-butoxy-2-isobutyl-1-oxo-1,2-  
dihydro-3-isoquinolinyl)methylcarbamate (0.23 g, 79.3%)  
as crystals.

Melting point 175-176°C.

15 Elemental analysis for  $C_{23}H_{35}N_3O_4$

Calculated: C, 66.16; H, 8.45; N, 10.06.

Found: C, 66.10; H, 8.74; N, 10.05.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.94 (6H, d,  $J=6.6$  Hz), 1.02 (3H, t,  
 $J=7.4$  Hz), 1.46 (9H, s), 1.50-1.64 (2H, m), 1.77-1.91  
20 (2H, m), 2.05-2.22 (1H, m), 3.82 (2H, t,  $J=6.6$  Hz), 3.93  
(2H, d,  $J=7.2$  Hz), 4.16 (2H, s), 4.47 (2H, d,  $J=5.4$  Hz),  
4.69 (1H, bs), 6.778-6.83 (2H, m), 8.21 (1H, d,  $J=9.2$   
Hz).

(3) 6-Amino-3-(aminomethyl)-4-butoxy-2-isobutyl-1(2H)-  
25 isoquinolinone dihydrochloride (synthesized according to  
the method similar to that in Example 1 (7))

Melting point 245-247°C.

Elemental analysis for  $C_{18}H_{29}N_3O_2Cl_2$

Calculated: C, 55.38; H, 7.49; N, 10.76.

30 Found: C, 55.02; H, 7.47; N, 10.72.

$^1\text{H-NMR}(\text{DMSO}-d_6)$   $\delta$ : 0.86 (6H, d,  $J=6.6$  Hz), 0.99 (3H, t,  
 $J=7.4$  Hz), 1.44-1.63 (2H, m), 1.77-2.02 (3H, m), 3.84-  
3.90 (4H, m), 4.11 (2H, d,  $J=4.0$  Hz), 6.30 (3H, bs),  
6.91-7.01 (2H, m), 8.00 (1H, d,  $J=9.2$  Hz), 8.60 (3H, bs).

35 **Example 83**

3-(Aminomethyl)-6-bromo-4-butoxy-2-neopentyl-1(2H)-

## isoquinolinone hydrochloride

(1) Ethyl 6-bromo-4-hydroxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (1))

5 Melting point 105-106°C.

Elemental analysis for  $C_{17}H_{20}NO_4Br$

Calculated: C, 53.42; H, 5.37; N, 3.66.

Found: C, 53.75; H, 5.25; N, 3.61.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.84 (9H, s), 1.47 (3H, t,  $J=7.2$  Hz),  
10 4.54 (2H, bs), 7.78 (1H, dd,  $J=1.8, 8.4$  Hz), 8.28 (1H, d,  $J=1.8$  Hz), 8.30 (1H, d,  $J=8.4$  Hz), 10.72 (1H, s).

(2) Ethyl 6-bromo-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (synthesized according to the method similar to that in Example 1 (2))

15 Melting point 107.5-108°C.

Elemental analysis for  $C_{21}H_{28}NO_4Br$

Calculated: C, 57.54; H, 6.44; N, 3.20.

Found: C, 57.54; H, 6.48; N, 3.18.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.93 (9H, s), 1.02 (3H, t,  $J=7.3$  Hz),  
20 1.44 (3H, t,  $J=7.2$  Hz), 1.44-1.61 (2H, m), 1.73-1.87 (2H, m), 3.94 (2H, t,  $J=6.6$  Hz), 4.06 (2H, bs), 4.43 (2H, q,  $J=7.2$  Hz), 7.65 (1H, dd,  $J=2.0, 8.6$  Hz), 7.89 (1H, d,  $J=2.0$  Hz), 8.28 (1H, d,  $J=8.6$  Hz).

(3) 6-Bromo-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-  
25 isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 4 (3))

Melting point 152-153°C.

Elemental analysis for  $C_{19}H_{24}NO_4Br$

Calculated: C, 55.62; H, 5.90; N, 3.41.

30 Found: C, 55.58; H, 5.80; N, 3.35.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.93 (9H, s), 1.01 (3H, t,  $J=7.3$  Hz),  
1.46-1.65 (2H, m), 1.76-1.90 (2H, m), 4.02 (2H, t,  $J=6.4$  Hz), 4.22 (2H, bs), 6.50 (1H, bs), 7.67 (1H, dd,  $J=2.0, 8.6$  Hz), 7.82 (1H, d,  $J=2.0$  Hz), 8.21 (1H, d,  $J=8.6$  Hz).

35 (4) 6-Bromo-4-butoxy-3-hydroxymethyl-2-neopentyl-1(2H)-isoquinolinone (synthesized according to the method

similar to that in Example 4 (4))

Melting point 162-163°C.

Elemental analysis for  $C_{19}H_{26}NO_3Br$

Calculated: C, 57.58; H, 6.61; N, 3.53.

5 Found: C, 57.60; H, 6.55; N, 3.49.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.95 (9H, s), 1.05 (3H, t,  $J=7.1$  Hz),  
1.51-1.69 (2H, m), 1.80-1.93 (2H, m), 2.88 (1H, t,  $J=5.8$   
Hz), 3.88 (2H, t,  $J=6.4$  Hz), 4.18 (2H, bs), 4.86 (2H,  
bs), 7.49 (1H, dd,  $J=1.8, 8.8$  Hz), 7.75 (1H, d,  $J=1.8$   
10 Hz), 8.08 (1H, d,  $J=8.8$  Hz).

(5) 6-Bromo-4-butoxy-3-chloromethyl-2-neopentyl-1(2H)-  
isoquinolinone (synthesized according to the method  
similar to that in Example 4 (5)).

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.98 (9H, s), 1.05 (3H, t,  $J=7.3$  Hz),  
15 1.52-1.70 (2H, m), 1.82-1.95 (2H, m), 3.94 (2H, t,  $J=6.4$   
Hz), 4.18 (2H, bs), 4.86 (2H, bs), 7.67 (1H, dd,  $J=1.8,$   
8.8 Hz), 7.87 (1H, d,  $J=1.8$  Hz), 8.28 (1H, d,  $J=8.8$  Hz).

(6) 2-[(6-Bromo-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-  
3-isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione

20 (synthesized according to the method similar to that in  
Example 4 (6))

Melting point 134-136°C.

Elemental analysis for  $C_{27}H_{29}N_2O_4Br$

Calculated: C, 61.72; H, 5.56; N, 5.33.

25 Found: C, 61.92; H, 5.49; N, 5.32.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.02 (9H, s), 1.02 (3H, t,  $J=7.3$  Hz),  
1.46-1.65 (2H, m), 1.82-1.96 (2H, m), 4.01 (2H, t,  $J=6.8$   
Hz), 4.05 (2H, bs), 5.07 (2H, s), 7.58 (1H, dd,  $J=2.0,$   
8.6 Hz), 7.60-7.84 (4H, m), 7.87 (1H, d,  $J=2.0$  Hz), 8.25  
30 (1H, d,  $J=8.6$  Hz).

(7) Tert-butyl (6-bromo-4-butoxy-2-neopentyl-1-oxo-1,2-  
dihydro-3-isoquinolinyl)methylcarbamate (synthesized  
according to the method similar to that in Example 1  
(6))

35 Melting point 130-131°C.

Elemental analysis for  $C_{24}H_{35}N_2O_4Br$

Calculated: C, 58.18; H, 7.12; N, 5.65.

Found: C, 58.50; H, 7.09; N, 5.56.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.99 (9H, s), 1.04 (3H, t, J=7.4 Hz),  
1.45 (9H, s), 1.46-1.68 (2H, m), 1.80-1.93 (2H, m), 3.85  
5 (2H, t, J=6.4 Hz), 4.14 (2H, bs), 4.56 (2H, d, J=5.4 Hz),  
4.71 (1H, bs), 7.58 (1H, dd, J=1.8, 8.4 Hz), 7.82 (1H, d,  
J=1.8 Hz), 8.24 (1H, d, J=8.4 Hz).

(8) 3-(Aminomethyl)-6-bromo-4-butoxy-2-neopentyl-1(2H)-  
isoquinolinone hydrochloride (synthesized according to  
10 the method similar to that in Example 1 (7))

Melting point 114-115°C.

Elemental analysis for C<sub>19</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>BrCl

Calculated: C, 52.85; H, 6.54; N, 6.49.

Found: C, 52.60; H, 6.62; N, 6.44.

15 <sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.90 (9H, s), 1.00 (3H, t, J=7.4 Hz),  
1.46-1.64 (2H, m), 1.77-1.90 (2H, m), 3.94 (2H, t, J=6.0  
Hz), 4.12 (2H, bs), 4.24 (2H, s), 7.79 (1H, dd, J=1.8,  
8.4 Hz), 7.87 (1H, d, J=1.8 Hz), 8.19 (1H, d, J=8.4 Hz),  
8.52 (3H, bs).

#### 20 Example 84

Methyl 3-(aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-  
dihydro-6-isoquinolinecarboxylate hydrochloride

(1) Methyl 4-butoxy-3-{{(tert-  
butoxycarbonyl)amino}methyl}-2-neopentyl-1-oxo-1,2-  
25 dihydro-6-isoquinolinecarboxylate (synthesized according

to the method similar to that in Example 75 (1))

Elemental analysis for C<sub>26</sub>H<sub>38</sub>N<sub>2</sub>O<sub>6</sub>

Calculated: C, 65.80; H, 8.07; N, 5.90.

Found: C, 66.03; H, 8.33; N, 6.05.

30 <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.00 (9H, s), 10.6 (3H, t, J=7.4 Hz),  
1.46 (9H, s), 1.53-1.71 (2H, m), 1.83-1.97 (2H, m), 3.90  
(2H, t, J=6.4 Hz), 3.99 (3H, s), 4.14 (2H, bs), 4.59 (2H,  
d, J=5.4 Hz), 4.79 (1H, bs), 8.06 (1H, dd, J=1.7, 8.4  
Hz), 8.38 (1H, d, J=1.7 Hz), 8.43 (1H, d, J=8.4 Hz).

35 (2) Methyl 3-(aminomethyl)-4-butoxy-2-neopentyl-1-oxo-  
1,2-dihydro-6-isoquinolinecarboxylate hydrochloride

(synthesized according to the method similar to that in Example 1 (7))

Melting point 123-124°C.

Elemental analysis for  $C_{21}H_{31}N_2O_4Cl$

5 Calculated: C, 61.38; H, 7.60; N, 6.82.

Found: C, 61.08; H, 7.82; N, 6.82.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.92 (9H, s), 1.02 (3H, t, J=7.3 Hz), 1.55-1.66 (2H, m), 1.79-1.91 (2H, m), 3.95 (3H, s), 3.97 (2H, t, J=6.2 Hz), 4.14 (2H, bs), 4.28 (2H, s), 8.11 (1H, dd, J=1.6, 8.6 Hz), 8.34 (1H, d, J=1.6 Hz), 8.40 (1H, d, J=8.6 Hz), 8.56 (3H, bs).

#### Example 85

3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid hydrochloride

15 (1) 4-Butoxy-3-{{{tert-butoxycarbonyl}amino}methyl}-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid (synthesized according to the method similar to that in Example 76 (1))

Melting point 130-131°C.

20 Elemental analysis for  $C_{25}H_{36}N_2O_6$

Calculated: C, 65.20; H, 7.88; N, 6.08.

Found: C, 64.92; H, 7.88; N, 6.04.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (9H, s), 1.08 (3H, t, J=7.3 Hz), 1.50 (9H, s), 1.56-1.73 (2H, m), 1.85-1.99 (2H, m), 3.90 (2H, t, J=6.2 Hz), 4.14 (2H, bs), 4.61 (2H, d, J=5.2 Hz), 5.64 (1H, bs), 8.31 (1H, d, J=8.4 Hz), 8.28-8.33 (2H, m).

25 (2) 3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid hydrochloride (synthesized according to the method similar to that in

30 Example 1 (7))

Melting point 255-257°C.

Elemental analysis for  $C_{20}H_{29}N_2O_4Cl$

Calculated: C, 60.52; H, 7.36; N, 7.06.

Found: C, 60.42; H, 7.35; N, 7.01.

35  $^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.92 (9H, s), 1.01 (3H, t, J=7.4 Hz), 1.54-1.66 (2H, m), 1.79-1.92 (2H, m), 3.97 (2H, t, J=6.3



Hz), 4.13 (2H, bs), 4.28 (2H, s), 8.09 (1H, dd, J=1.5, 8.4 Hz), 8.33 (1H, bs), 8.34 (1H, d, J=1.5 Hz), 8.38 (1H, d, J=8.4 Hz), 8.60 (3H, bs).

**Example 86**

5 3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide hydrochloride

(1) Tert-butyl {(6-aminocarbonyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl}methylcarbamate  
(synthesized according to the method similar to that in

10 Example 77 (1))

Melting point 172-173°C.

Elemental analysis for  $C_{25}H_{37}N_3O_5 \cdot 1/2(i-Pr)_2O$

Calculated: C, 65.86; H, 8.49; N, 8.23.

Found: C, 65.53; H, 8.75; N, 8.17.

15  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (9H, s), 1.04 (3H, t, J=7.2 Hz), 1.46 (9H, s), 1.47-1.68 (2H, m), 1.81-1.95 (2H, m), 3.71 (2H, t, J=6.2 Hz), 4.14 (2H, bs), 4.58 (2H, d, J=5.6 Hz), 4.97 (1H, bs), 5.91 (1H, bs), 6.39 (1H, bs), 7.75 (1H, dd, J=1.6, 8.4 Hz), 8.12 (1H, d, J=8.4 Hz), 8.36 (1H, d, J=8.4 Hz).

(2) 3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide hydrochloride  
(synthesized according to the method similar to that in Example 1 (7)).

25 Melting point 237-238°C.

Elemental analysis for  $C_{26}H_{30}N_3O_3Cl \cdot 1/2H_2O$

Calculated: C, 59.32; H, 7.72; N, 10.38.

Found: C, 59.45; H, 7.63; N, 10.20.

30  $^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.91 (9H, s), 1.00 (3H, t, J=7.4 Hz), 1.48-1.67 (2H, m), 1.80-1.92 (2H, m), 3.98 (2H, t, J=6.4 Hz), 4.12 (2H, bs), 4.26 (2H, s), 7.70 (1H, s), 8.04 (1H, dd, J=1.2, 8.2 Hz), 8.22 (1H, d, J=1.2 Hz), 8.33 (1H, d, J=8.2 Hz), 8.37 (1H, s), 8.58 (3H, bs).

**Example 87**

35 3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinecarbonitrile hydrochloride

(1) Tert-butyl (4-butoxy-6-cyano-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 78 (7))

5 Melting point 162-163°C.

Elemental analysis for  $C_{25}H_{35}N_3O_4$ .

Calculated: C, 68.00; H, 7.99; N, 9.52.

Found: C, 67.97; H, 8.13; N, 9.44.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.00 (9H, s), 1.05 (3H, t,  $J=7.3$  Hz),  
10 1.45 (9H, s), 1.53-1.68 (2H, m), 1.82-1.90 (2H, m), 3.86  
(2H, t,  $J=6.6$  Hz), 4.17 (2H, bs), 4.58 (2H, d,  $J=5.4$  Hz),  
4.70 (1H, bs), 7.68 (1H, dd,  $J=1.6, 8.8$  Hz), 8.00 (1H, d,  
 $J=1.6$  Hz), 8.49 (1H, d,  $J=8.2$  Hz).

(2) 3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-  
15 dihydro-6-isoquinolinecarbonitrile hydrochloride  
(synthesized according to the method similar to that in  
Example 1 (7))

Elemental analysis for  $C_{20}H_{28}N_3O_2Cl \cdot 1/4H_2O$ .

Calculated: C, 62.81; H, 7.51; N, 10.99.

20 Found: C, 62.98; H, 7.75; N, 10.95.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.91 (9H, s), 1.00 (3H, t,  $J=7.1$  Hz),  
1.46-1.64 (2H, m), 1.80-1.92 (2H, m), 3.97 (2H, t,  $J=6.4$   
Hz), 4.14 (2H, bs), 4.27 (2H, bs), 7.97 (1H, dd,  $J=1.2,$   
8.0 Hz), 8.23 (1H, d,  $J=1.2$  Hz), 8.41 (1H, d,  $J=8.0$  Hz),  
25 8.68 (3H, bs).

#### Example 88

N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-  
dihydro-6-isoquinolinyl}acetamide hydrochloride

(1) A solution of tert-butyl (6-amino-4-butoxy-2-  
30 isobutyl-1-oxo-1,2-dihydro-3-  
isoquinolinyl)methylcarbamate (synthesized according to  
the method similar to that in Example 82 (2)) (0.21 g,  
0.5 mmol) and acetyl chloride (0.04 ml, 0.6 mmol) in  
N,N-dimethylacetamide (10 ml) was stirred at room  
35 temperature for 2 h. The reaction mixture was poured  
into water and extracted with ethyl acetate. The

extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl {6-  
5 (acetylamino)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.19 g, 80.8%) as crystals.

Melting point 174-175°C.

Elemental analysis for  $C_{25}H_{37}N_3O_5$

10 Calculated: C, 65.34; H, 8.11; N, 9.14.

Found: C, 65.32; H, 8.05; N, 9.21.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.95 (6H, d,  $J=6.6$  Hz), 1.02 (3H, t,  $J=7.4$  Hz), 1.47 (9H, s), 1.47-1.65 (2H, m), 1.81-1.95 (2H, m), 2.09-2.20 (1H, m), 2.26 (3H, s), 3.88 (2H, t,  $J=6.6$  Hz);  
15 3.98 (2H, d,  $J=7.4$  Hz), 4.51 (2H, d,  $J=5.6$  Hz), 4.82 (1H, bs), 7.35 (1H, d,  $J=8.0$  Hz), 7.71 (1H, bs), 8.17 (1H, s), 8.32 (1H, d,  $J=8.0$  Hz).

(2) N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl}acetamide hydrochloride

20 (synthesized according to the method similar to that in Example 1 (7))

Melting point 176-177°C.

Elemental analysis for  $C_{20}H_{30}N_3O_3Cl \cdot H_2O$

Calculated: C, 58.03; H, 7.79; N, 10.15.

25 Found: C, 58.26; H, 8.11; N, 10.08.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.87 (6H, d,  $J=6.6$  Hz), 0.99 (3H, t,  $J=7.3$  Hz), 1.50-1.62 (2H, m), 1.79-2.04 (3H, m), 2.14 (3H, s), 3.91 (2H, t,  $J=6.8$  Hz), 3.93 (2H, d,  $J=7.0$  Hz), 4.16 (2H, d,  $J=5.4$  Hz), 7.70 (1H, dd,  $J=2.0, 8.8$  Hz),  
30 8.18 (1H, d,  $J=8.8$  Hz), 8.27 (1H, d,  $J=2.0$  Hz), 8.56 (3H, bs), 10.59 (1H, s).

#### Example 89

N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl}propanamide hydrochloride

35 (1) tert-butyl {4-butoxy-2-isobutyl-1-oxo-6-(propionylamino)-1,2-dihydro-3-

isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 88 (1))

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.95 (6H, d, J=7.0 Hz), 1.01 (3H, t, J=7.2 Hz), 1.28 (3H, t, J=7.6 Hz), 1.46 (9H, s), 1.47-1.67 (2H, m), 1.80-1.94 (2H, m), 2.09-2.27 (1H, m), 2.48 (2H, q, J=7.6 Hz), 3.88 (2H, t, J=6.4 Hz), 3.98 (2H, d, J=7.4 Hz), 4.51 (2H, d, J=5.0 Hz), 4.83 (1H, bs), 7.37 (1H, dd, J=1.8, 8.8 Hz), 7.69 (1H, bs), 8.15 (1H, d, J=1.8 Hz), 8.31 (1H, d, J=8.8 Hz).

(2) N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl}propanamide hydrochloride (synthesized according to the method similar to that in Example 1 (7)).

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ:0.87 (6H, d, J=7.0 Hz), 1.00 (6H, m), 1.46-1.64 (2H, m), 1.72-2.14 (3H, m), 2.41-2.50 (2H, m), 3.91 (4H, bs), 4.16 (2H, s), 7.72 (1H, d, J=9.0 Hz), 8.18 (1H, d, J=9.0 Hz), 8.27 (1H, s), 8.55 (3H, bs), 10.49 (1H, s).

#### Example 90

N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl}-2-methylpropanamide hydrochloride

(1) Tert-butyl {4-butoxy-2-isobutyl-6-(isobutyrylamino)-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 88 (1)).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.95 (6H, d, J=7.0 Hz), 1.02 (3H, t, J=7.2 Hz), 1.29 (6H, d, J=7.0 Hz), 1.46 (9H, s), 1.47-1.66 (2H, m), 1.80-1.91 (2H, m), 2.09-2.20 (1H, m), 2.53-2.66 (1H, m), 3.89 (2H, t, J=6.6 Hz), 3.98 (2H, d, J=7.4 Hz), 4.51 (2H, d, J=5.6 Hz), 4.79 (1H, bs), 7.41 (1H, dd, J=1.8, 8.8 Hz), 7.62 (1H, bs), 8.15 (1H, d, J=1.8 Hz), 8.32 (1H, d, J=8.8 Hz).

(2) N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl}-2-methylpropanamide hydrochloride (synthesized according to the method

similar to that in Example 1 (7))

Melting point 181-183°C.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ:0.88 (6H, d, J=6.2 Hz), 1.00 (3H, t, J=7.4 Hz), 1.14 (6H, d, J=6.6 Hz), 1.48-1.64 (2H, m),  
5 1.83-2.12 (3H, m), 2.62-2.78 (1H, m), 3.92-3.95 (4H, m),  
4.16 (2H, bs), 7.76 (1H, d, J=8.8 Hz), 8.18 (1H, d, J=8.8 Hz), 8.27 (1H, s), 8.57 (3H, bs), 10.47 (1H, s).

#### Example 91

N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-  
10 dihydro-6-isoquinolinyl}benzamide hydrochloride  
(1) Tert-butyl {4-butoxy-6-(benzoylamino)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl}methylcarbamate

(synthesized according to the method similar to that in Example 88 (1))

15 <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.95 (6H, d, J=6.6 Hz), 1.02 (3H, t, J=7.4 Hz), 1.47 (9H, s), 1.48-1.68 (2H, m), 1.82-1.96 (2H, m), 2.07-2.23 (1H, m), 3.92 (2H, t, J=6.8 Hz), 3.98 (2H, d, J=8.8 Hz), 4.52 (2H, d, J=5.4 Hz), 4.89 (1H, bs),  
20 7.45-7.62 (4H, m), 7.90-7.94 (2H, m), 8.25 (1H, bs),  
7.56 (1H, bs), 8.27 (1H, d, J=1.8 Hz), 8.32 (1H, d, J=8.8 Hz).

(2) N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl}benzamide hydrochloride  
(synthesized according to the method similar to that in

25 Example 1 (7))  
<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ:0.89 (6H, d, J=6.6 Hz), 1.01 (3H, t, J=7.3 Hz), 1.49-1.67 (2H, m), 1.83-2.06 (3H, m), 3.93-3.98 (4H, m), 4.19 (2H, s), 7.54-7.68 (3H, m), 7.95-8.03 (3H, m), 8.25 (1H, d, J=8.8 Hz), 8.43 (1H, d, J=1.8 Hz),  
30 8.58 (3H, bs), 10.77 (1H, s).

#### Example 92

N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl}cyclopentanecarboxamide hydrochloride

35 (1) Tert-butyl {4-butoxy-6-((cyclopentylcarbonyl)amino)-2-isobutyl-1-oxo-1,2-dihydro-3-

isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 88 (1))

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.95 (6H, d, J=7.0 Hz), 1.02 (3H, t, J=7.3 Hz), 1.46 (9H, s), 1.47-1.74 (4H, m), 1.78-2.20 (9H, m), 2.67-2.80 (1H, m), 3.89 (2H, t, J=6.6 Hz), 3.98 (2H, d, J=7.6 Hz), 4.51 (2H, d, J=5.4 Hz), 4.78 (1H, bs), 7.42 (1H, dd, J=2.2, 8.8 Hz), 7.56 (1H, bs), 8.12 (1H, d, J=2.2 Hz), 8.32 (1H, d, J=8.8 Hz).

(2) N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl}cyclopentanecarboxamide (synthesized according to the method similar to that in Example 1 (7))

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ:0.87 (6H, d, J=6.2 Hz), 0.99 (3H, t, J=7.1 Hz), 1.54-2.11 (11H, m), 2.79-2.92 (1H, m), 3.91-3.95 (4H, m), 4.16 (2H, s), 7.75 (1H, d, J=8.8 Hz), 8.18 (1H, d, J=8.8 Hz), 8.25 (1H, s), 8.55 (3H, bs), 10.49 (1H, s).

#### Example 93

N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl}methanesulfonamide hydrochloride (1) Tert-butyl {4-butoxy-2-isobutyl-6-

{(methylsulfonyl)amino}-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 88 (1))

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.95 (6H, d, J=6.6 Hz), 1.02 (3H, t, J=7.4 Hz), 1.47 (9H, s), 1.47-1.64 (2H, m), 1.79-1.94 (2H, m), 2.10-2.23 (1H, m), 3.11 (3H, s), 3.86 (2H, t, J=6.6 Hz), 3.99 (2H, d, J=7.8 Hz), 4.51 (2H, d, J=5.4 Hz), 4.77 (1H, bs), 7.23 (1H, dd, J=2.0, 8.6 Hz), 7.31 (1H, s), 7.56 (1H, d, J=2.0 Hz), 8.38 (1H, d, J=8.6 Hz).

(2) N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl}methanesulfonamide (synthesized according to the method similar to that in Example 1 (7))

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ:0.87 (6H, d, J=6.6 Hz), 0.99 (3H, t, J=7.8 Hz), 1.45-1.64 (2H, m), 1.78-2.09 (3H, m), 3.13

(3H, s), 3.88-3.94 (4H, m), 4.17 (2H, bs), 7.40 (1H, dd, J=2.0, 8.8 Hz), 7.60 (1H, d, J=2.0 Hz), 8.21 (1H, d, J=8.8 Hz), 8.58 (3H, bs), 10.57 (1H, s).

**Example 94**

- 5 N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl}benzenesulfonamide hydrochloride  
(1) Tert-butyl {4-butoxy-2-isobutyl-1-oxo-6-  
{(phenylsulfonyl)amino}-1,2-dihydro-3-  
isoquinolinyl}methylcarbamate (synthesized according to  
10 the method similar to that in Example 88 (1))  
Melting point 160-161°C.

Elemental analysis for  $C_{29}H_{39}N_3O_6S$

Calculated: C, 62.45; H, 7.05; N, 7.53.

Found: C, 62.35; H, 6.97; N, 7.50.

- 15  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.93 (6H, d, J=6.6 Hz), 1.02 (3H, t, J=7.3 Hz), 1.46 (9H, s), 1.47-1.63 (2H, m), 1.72-1.90 (2H, m), 2.07-2.20 (1H, m), 3.76 (2H, t, J=6.6 Hz), 3.96 (2H, d, J=7.6 Hz), 4.48 (2H, d, J=5.6 Hz), 4.78 (1H, bs), 7.14 (1H, d, J=8.4 Hz), 7.41-7.58 (4H, m), 7.81-7.99 (3H, m), 8.25 (1H, dd, J=1.4, 8.4 Hz).

- 20 (2) N-{3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl}benzenesulfonamide (synthesized according to the method similar to that in Example 1 (7))

- 25 Melting point 166-167°C.

Elemental analysis for  $C_{24}H_{32}N_3O_4ClS \cdot 1/4H_2O$

Calculated: C, 57.82; H, 6.57; N, 8.43.

Found: C, 57.83; H, 6.49; N, 8.26.

- 30  $^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.84 (6H, d, J=7.4 Hz), 1.01 (3H, t, J=7.4 Hz), 1.43-1.62 (2H, m), 1.75-1.99 (3H, m), 3.76 (2H, t, J=6.6 Hz), 3.89 (2H, d, J=6.8 Hz), 4.11 (2H, bs), 7.35 (1H, dd, J=2.0, 8.6 Hz), 7.53-7.65 (3H, m), 7.83-7.88 (2H, m), 8.13 (1H, d, J=8.6 Hz), 8.52 (3H, bs), 11.18 (1H, s).

- 35 **Example 95**

2-{3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-

dihydro-6-isoquinolinyl}oxy}acetamide hydrochloride

(1) A solution of tert-butyl (4-butoxy-6-hydroxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (Example 59 (1)) (0.43 g, 1 mmol), iodoacetamide (0.22 g, 1.2 mmol) and 1,8-diazabicyclo[5.4.0]-7-undecene (0.18 ml, 1.2 mmol) in N,N-dimethylformamide (10 ml) was stirred at 70°C for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl {6-(2-amino-2-oxoethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl}-methylcarbamate (0.29 g, 60.4%) as crystals. Melting point 114-115°C.

Elemental analysis for  $C_{26}H_{39}N_3O_6$

Calculated: C, 63.78; H, 8.03; N, 8.58.

Found: C, 63.61; H, 7.91; N, 8.43.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (9H, s), 1.04 (3H, t, J=7.0 Hz), 1.43 (9H, s), 1.45-1.67 (2H, m), 1.79-1.90 (2H, m), 3.85 (2H, t, J=6.6 Hz), 4.14 (2H, bs), 4.56 (2H, d, J=5.4 Hz), 4.57 (1H, bs), 7.07-7.12 (2H, m), 8.36 (1H, d, J=9.4 Hz).

(2) 2-{{3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl}oxy}acetamide hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Melting point 233-235°C.

Elemental analysis for  $C_{21}H_{32}N_3O_4Cl \cdot 1/2H_2O$

Calculated: C, 57.99; H, 7.65; N, 9.66.

Found: C, 58.18; H, 7.68; N, 9.63.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.89 (9H, s), 1.00 (3H, t, J=7.3 Hz), 1.50-1.65 (2H, m), 1.77-1.91 (2H, m), 3.92 (2H, t, J=6.4 Hz), 4.07 (2H, bs), 4.22 (2H, d, J=4.4 Hz), 4.64 (2H, s), 7.07 (1H, d, J=2.6 Hz), 7.22 (1H, dd, J=2.6, 8.8 Hz), 7.46 (1H, bs), 7.73 (1H, bs), 8.20 (1H, d, J=8.8 Hz),



8.54 (3H, bs).

**Example 96**

3-(Aminomethyl)-4-butoxy-6-isopropoxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride

- 5 (1) Tert-butyl (4-butoxy-6-isopropoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 95

(1))

Melting point 130-130.5°C.

- 10 Elemental analysis for  $C_{27}H_{42}N_2O_5$

Calculated: C, 68.32; H, 8.92; N, 5.90.

Found: C, 68.28; H, 8.75; N, 5.99.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (9H, s), 1.03 (3H, t,  $J=7.4$  Hz), 1.41 (6H, d,  $J=5.8$  Hz), 1.45 (9H, s), 1.46-1.65 (2H, m),

- 15 1.79-1.93 (2H, m), 3.86 (2H, t,  $J=6.4$  Hz), 4.14 (2H, bs), 4.55 (2H, d,  $J=4.8$  Hz), 4.64-4.76 (2H, m), 7.00-7.04 (2H, m), 8.31 (1H, d,  $J=9.6$  Hz).

(2) 3-(Aminomethyl)-4-butoxy-6-isopropoxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride (synthesized

- 20 according to the method similar to that in Example 1

(7))

Melting point 181-182°C.

Elemental analysis for  $C_{22}H_{35}N_2O_3Cl$

Calculated: C, 64.29; H, 8.58; N, 6.82.

- 25 Found: C, 64.10; H, 8.80; N, 6.78.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.90 (9H, s), 1.00 (3H, t,  $J=7.1$  Hz), 1.35 (6H, d,  $J=6.2$  Hz), 1.51-1.62 (2H, m), 1.77-1.90 (2H, m), 3.93 (2H, t,  $J=6.3$  Hz), 4.07 (2H, bs), 4.22 (2H, bs), 4.74-4.86 (1H, m), 7.05 (1H, d,  $J=2.4$  Hz), 7.16 (1H, dd,

- 30  $J=2.4, 8.8$  Hz), 8.17 (1H, d,  $J=8.8$  Hz), 8.52 (3H, bs).

**Example 97**

3-(Aminomethyl)-4-butoxy-2-neopentyl-6-(2,2,2-trifluoroethoxy)-1(2H)-isoquinolinone hydrochloride

- (1) Tert-butyl {4-butoxy-2-neopentyl-6-(2,2,2-trifluoroethoxy)-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to

the method similar to that in Example 95 (1))

Melting point 154.5-155°C.

Elemental analysis for  $C_{26}H_{37}N_2O_5F_3$

Calculated: C, 60.69; H, 7.25; N, 5.44.

5 Found: C, 60.44; H, 7.16; N, 5.48.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (9H, s), 1.04 (3H, t, J=7.0 Hz),  
1.45 (9H, s), 1.46-1.64 (2H, m), 1.80-1.90 (2H, m), 3.86  
(2H, t, J=6.6 Hz), 4.11 (2H, bs), 4.48 (2H, q, J=8.0 Hz),  
4.56 (2H, d, J=5.6 Hz), 4.71 (1H, bs), 7.09-7.13 (2H, m),  
10 8.37 (1H, d, J=8.0 Hz).

(2) 3-(Aminomethyl)-4-butoxy-2-neopentyl-6-(2,2,2-  
trifluoroethoxy)-1(2H)-isoquinolinone hydrochloride  
(synthesized according to the method similar to that in  
Example 1 (7))

15 Melting point 145.5-146°C.

Elemental analysis for  $C_{21}H_{30}N_2O_3ClF_3 \cdot 1/2H_2O$

Calculated: C, 54.84; H, 6.79; N, 6.09.

Found: C, 54.75; H, 6.77; N, 6.22.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.90 (9H, s), 0.99 (3H, t, J=7.3 Hz),  
20 1.47-1.65 (2H, m), 1.78-1.89 (2H, m), 3.95 (2H, t, J=6.4  
Hz), 4.08 (2H, bs), 4.24 (2H, bs), 5.02 (2H, q, J=8.8  
Hz), 7.18 (1H, d, J=2.6 Hz), 7.32 (1H, dd, J=2.6, 8.8  
Hz), 8.24 (1H, d, J=8.8 Hz), 8.52 (3H, bs).

#### Example 98

25 3-(Aminomethyl)-4-butoxy-6-(cyclopropylmethoxy)-2-  
neopentyl-1(2H)-isoquinolinone hydrochloride

(1) Tert-butyl {4-butoxy-6-(cyclopropylmethoxy)-2-  
neopentyl-1-oxo-1,2-dihydro-3-  
isoquinolinyl)methylcarbamate (synthesized according to

30 the method similar to that in Example 95 (1))

Melting point 154-155°C.

Elemental analysis for  $C_{28}H_{42}N_2O_5 \cdot 1/2H_2O$

Calculated: C, 67.85; H, 8.74; N, 5.65.

Found: C, 68.08; H, 8.65; N, 5.47.

35  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.36-0.42 (2H, m), 0.65-0.75 (2H, m),  
0.99 (9H, s), 1.03 (3H, t, J=7.4 Hz), 1.22-1.37 (1H, m),

1.45 (9H, s), 1.52-1.68 (2H, m), 1.78-1.93 (2H, m), 3.86 (2H, t, J=6.4 Hz), 3.92 (2H, d, J=6.8 Hz), 4.10 (2H, bs), 4.55 (2H, d, J=5.2 Hz), 4.63 (1H, bs), 7.04-7.10 (2H, m), 8.30-8.34 (1H, m).

- 5 (2) 3-(Aminomethyl)-4-butoxy-6-(cyclopropylmethoxy)-2-neopentyl-1(2H)-isoquinolinone hydrochloride  
(synthesized according to the method similar to that in Example 1 (7))

Melting point 203-205°C.

- 10 Elemental analysis for  $C_{23}H_{35}N_2O_3Cl$

Calculated: C, 65.31; H, 8.34; N, 6.62.

Found: C, 65.23; H, 8.25; N, 6.71.

- $^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.34-0.42 (2H, m), 0.58-0.67 (2H, m), 0.89 (9H, s), 0.99 (3H, t, J=7.3 Hz), 1.23-1.33 (1H, m),  
15 1.52-1.63 (2H, m), 1.77-1.87 (2H, m), 3.93 (2H, t, J=6.2 Hz), 3.99 (2H, d, J=7.0 Hz), 4.03 (2H, bs), 4.23 (2H, s), 7.06 (1H, d, J=2.4 Hz), 7.19 (1H, dd, J=2.4, 9.0 Hz), 8.18 (1H, d, J=9.0 Hz), 8.50 (3H, bs).

#### Example 99

- 20 3-(Aminomethyl)-4-butoxy-2-neopentyl-6-(2-propynyloxy)-1(2H)-isoquinolinone hydrochloride

(1) Tert-butyl {4-butoxy-2-neopentyl-1-oxo-6-(2-propynyloxy)-1,2-dihydro-3-isoquinolinyl}methylcarbamate  
(synthesized according to the method similar to that in

- 25 Example 95 (1))

- $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (9H, s), 1.03 (3H, t, J=7.4 Hz), 1.45 (9H, s), 1.53-1.68 (2H, m), 1.80-1.94 (2H, m), 2.57 (1H, t, J=2.2 Hz), 3.87 (2H, t, J=6.4 Hz), 4.10 (2H, bs), 4.56 (2H, d, J=4.8 Hz), 4.63 (1H, bs), 4.82 (2H, d, J=2.2 Hz), 7.11 (1H, dd, J=2.4, 8.8 Hz), 7.19 (1H, d, J=2.4 Hz), 8.35 (1H, d, J=8.8 Hz).

(2) 3-(Aminomethyl)-4-butoxy-2-neopentyl-6-(2-propynyloxy)-1(2H)-isoquinolinone hydrochloride  
(synthesized according to the method similar to that in

- 35 Example 1 (7))

Elemental analysis for  $C_{22}H_{31}N_2O_3Cl \cdot 1/4H_2O$

Calculated: C, 64.22; H, 7.72; N, 6.81.

Found: C, 64.36; H, 7.73; N, 6.66.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ:0.90 (9H, s), 1.00 (3H, t, J=7.4 Hz), 1.53-1.64 (2H, m), 1.79-1.91 (2H, m), 3.71 (1H, t, J=2.2 Hz), 3.95 (2H, t, J=6.1 Hz), 4.08 (2H, bs), 4.23 (2H, s), 5.01 (1H, d, J=2.2 Hz), 7.19-7.23 (2H, m), 8.20 (1H, d, J=9.6 Hz), 8.50 (3H, bs).

#### Example 100

3-(Aminomethyl)-4-butoxy-6-isobutoxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride

(1) Tert-butyl (4-butoxy-6-isobutoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (synthesized according to the method similar to that in Example 95 (1))

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.99 (9H, s), 1.04 (3H, t, J=7.2 Hz), 1.06 (6H, d, J=6.4 Hz), 1.45 (9H, s), 1.51-1.69 (2H, m), 1.79-1.93 (2H, m), 2.09-2.22 (1H, m), 3.84 (2H, d, J=6.6 Hz), 3.86 (2H, t, J=6.5 Hz), 4.10 (2H, bs), 4.56 (2H, d, J=5.6 Hz), 4.69 (1H, bs), 7.04-7.08 (2H, m), 8.31 (1H, d, J=9.4 Hz).

(2) 3-(Aminomethyl)-4-butoxy-6-isobutoxy-2-neopentyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method similar to that in Example 1 (7))

Elemental analysis for C<sub>23</sub>H<sub>37</sub>N<sub>2</sub>O<sub>3</sub>Cl 1/4H<sub>2</sub>O

Calculated: C, 64.32; H, 8.80; N, 6.52.

Found: C, 64.31; H, 8.87; N, 6.60.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ:0.89 (9H, s), 1.00 (3H, t, J=7.0 Hz), 1.02 (6H, d, J=6.6 Hz), 1.50-1.68 (2H, m), 1.77-1.87 (2H, m), 2.03-2.16 (1H, m), 3.92 (2H, d, J=6.6 Hz), 3.93 (2H, t, J=6.2 Hz), 4.04 (2H, bs), 4.23 (2H, s), 7.07 (1H, d, J=2.6 Hz), 7.19 (1H, dd, J=2.6, 8.8 Hz), 8.18 (1H, d, J=8.8 Hz), 8.45 (3H, bs).

#### Example 101

3-(Aminomethyl)-4-butoxy-6-(cyclopentyloxy)-2-neopentyl-1(2H)-isoquinolinone hydrochloride

(1) Tert-butyl {4-butoxy-6-(cyclopentyloxy)-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl}methylcarbamate  
(synthesized according to the method similar to that in Example 95 (1))

5 <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.99 (9H, s), 1.03 (3H, t, J=7.4 Hz), 1.45 (9H, s), 1.50-1.70 (4H, m), 1.73-1.98 (8H, m), 3.86 (2H, t, J=6.4 Hz), 4.10 (2H, bs), 4.55 (2H, d, J=5.2 Hz), 4.68 (1H, bs), 4.86-4.90 (1H, m), 6.98-7.04 (2H, m), 8.27-8.32 (1H, m).

10 (2) 3-(Aminomethyl)-4-butoxy-6-(cyclopentyloxy)-2-neopentyl-1(2H)-isoquinolinone hydrochloride  
(synthesized according to the method similar to that in Example 1 (7))

Elemental analysis for C<sub>24</sub>H<sub>37</sub>N<sub>2</sub>O<sub>3</sub>Cl 1/4H<sub>2</sub>O

15 Calculated: C, 65.29; H, 8.56; N, 6.34.

Found: C, 65.27; H, 8.53; N, 6.18.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ:0.89 (9H, s), 1.00 (3H, t, J=7.3 Hz), 1.52-2.05 (12H, m), 3.93 (2H, t, J=6.2 Hz), 4.05 (2H, bs), 4.23 (2H, s), 4.99 (1H, bs), 7.04 (1H, d, J=2.4 Hz), 20 7.13 (1H, dd, J=2.4, 9.0 Hz), 8.16 (1H, d, J=9.0 Hz), 8.51 (3H, bs).

#### Example 102

3-(Aminomethyl)-4-butoxy-6-(cyclohexylmethoxy)-2-neopentyl-1(2H)-isoquinolinone hydrochloride

25 (1) Tert-butyl {4-butoxy-6-(cyclohexylmethoxy)-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl}methylcarbamate (synthesized according to the method similar to that in Example 95 (1))

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.99 (9H, s), 1.04 (3H, t, J=7.3 Hz), 30 1.07-1.35 (3H, m), 1.45 (9H, s), 1.51-1.93 (8H, m), 3.83-3.89 (4H, m), 4.10 (2H, bs), 4.55 (2H, d, J=5.2 Hz), 4.63 (1H, bs), 7.03-7.08 (2H, m), 8.31 (1H, d, J=8.4 Hz).

(2) 3-(Aminomethyl)-4-butoxy-6-(cyclohexylmethoxy)-2-neopentyl-1(2H)-isoquinolinone hydrochloride

35 (synthesized according to the method similar to that in Example 1 (7))

Elemental analysis for  $C_{26}H_{41}N_2O_3Cl$

Calculated: C, 67.15; H, 8.89; N, 6.02.

Found: C, 67.00; H, 8.83; N, 6.03.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.89 (9H, s), 1.00 (3H, t,  $J=7.3$  Hz),  
5 1.09-1.30 (3H, m), 1.53-1.84 (12H, m), 3.90-3.97 (4H, m),  
4.08 (2H, bs), 4.23 (2H, s), 7.06 (1H, d,  $J=2.3$  Hz),  
7.18 (1H, dd,  $J=2.3, 8.8$  Hz), 8.18 (1H, d,  $J=8.8$  Hz),  
8.47 (3H, bs).

#### Example 103

10 3-(Aminomethyl)-4-butoxy-6-(3,3-dimethyl-2-oxobutoxy)-2-neopentyl-1(2H)-isoquinolinone hydrochloride

(1) Tert-butyl {4-butoxy-6-(3,3-dimethyl-2-oxobutoxy)-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl}methylcarbamate (synthesized according to  
15 the method similar to that in Example 95 (1))

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.98 (9H, s), 1.03 (3H, t,  $J=7.2$  Hz),  
1.29 (9H, s), 1.45 (9H, s), 1.51-1.65 (2H, m), 1.76-1.87  
(2H, m), 3.87 (2H, t,  $J=6.4$  Hz), 4.10 (2H, bs), 4.54 (2H,  
d,  $J=5.2$  Hz), 4.69 (1H, bs), 5.01 (2H, s), 6.98 (1H, d,  
20  $J=2.6$  Hz), 7.05 (1H, dd,  $J=2.6, 8.8$  Hz), 8.33 (1H, d,  
 $J=8.8$  Hz).

(2) 3-(Aminomethyl)-4-butoxy-6-(3,3-dimethyl-2-oxobutoxy)-2-neopentyl-1(2H)-isoquinolinone hydrochloride (synthesized according to the method  
25 similar to that in Example 1 (7))

Elemental analysis for  $C_{25}H_{39}N_2O_4Cl \cdot 1/4H_2O$

Calculated: C, 63.68; H, 8.44; N, 5.94.

Found: C, 63.64; H, 8.32; N, 5.99.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.89 (9H, s), 0.98 (3H, t,  $J=7.2$  Hz),  
30 1.21 (9H, s), 1.48-1.59 (2H, m), 1.73-1.84 (2H, m), 3.90  
(2H, t,  $J=6.5$  Hz), 4.05 (2H, bs), 4.21 (2H, s), 5.39 (2H,  
s), 6.90 (1H, d,  $J=2.5$  Hz), 7.17 (1H, dd,  $J=2.5, 8.9$  Hz),  
8.18 (1H, d,  $J=8.9$  Hz), 8.43 (3H, bs).

#### Example 104

35 Ethyl {3-(aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl}oxy}acetate hydrochloride

(1) Ethyl {4-butoxy-3-{{{tert-butoxycarbonyl}amino}methyl}-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl}oxy}acetate (synthesized according to the method similar to that in Example 95

5 (1))

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.98 (9H, s), 1.04 (3H, t, J=7.3 Hz), 1.30 (3H, t, J=7.1 Hz), 1.45 (9H, s), 1.52-1.67 (4H, m), 1.78-1.88 (2H, m), 3.84 (2H, t, J=6.6 Hz), 4.14 (2H, bs), 4.29 (2H, q, J=7.1 Hz), 4.55 (2H, d, J=5.2 Hz), 4.64 (1H, 10 bs), 4.74 (2H, s), 7.02 (1H, d, J=1.5 Hz), 7.08 (1H, dd, J=1.5, 8.8 Hz), 8.33 (1H, d, J=8.8 Hz).

(2) Ethyl {{3-(aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl}oxy}acetate hydrochloride (synthesized according to the method similar to that in 15 Example 1 (7))

Elemental analysis for C<sub>23</sub>H<sub>35</sub>N<sub>2</sub>O<sub>5</sub>Cl 1/2H<sub>2</sub>O

Calculated: C, 59.54; H, 7.82; N, 6.04.

Found: C, 59.81; H, 7.70; N, 5.99.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ:0.89 (9H, s), 1.00 (3H, t, J=7.1 Hz), 20 1.23 (3H, t, J=7.1 Hz), 1.50-1.61 (4H, m), 1.78-1.91 (2H, m), 3.91 (2H, t, J=6.2 Hz), 4.01 (2H, bs), 4.19 (2H, q, J=7.1 Hz), 4.21 (2H, s), 5.01 (2H, s), 6.99 (1H, d, J=2.6 Hz), 7.22 (1H, dd, J=2.6, 9.0 Hz), 8.20 (1H, d, J=9.0 Hz), 8.42 (3H, bs).

25 **Example 105**

3-(Aminomethyl)-4-butoxy-6-(1-methyl-2-oxopropoxy)-2-neopentyl-1(2H)-isoquinolinone hydrochloride

(1) Tert-butyl {4-butoxy-6-(1-methyl-2-oxopropoxy)-2-neopentyl-1-oxo-1,2-dihydro-3- 30 isoquinolinyl}methylcarbamate (synthesized according to the method similar to that in Example 95 (1))

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<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.99 (9H, s), 1.04 (3H, t, J=7.3 Hz), 1.44 (9H, s), 1.52-1.70 (5H, m), 1.78-1.92 (2H, m), 2.19 35 (3H, s), 3.89 (2H, t, J=6.4 Hz), 4.11 (2H, bs), 4.57 (2H, d, J=5.4 Hz), 4.73 (1H, bs), 7.08-7.17 (2H, m), 8.38 (1H,

d, J=8.8 Hz).

(2) 3-(Aminomethyl)-4-butoxy-6-(1-methyl-2-oxopropoxy)-2-neopentyl-1(2H)-isoquinolinone hydrochloride

(synthesized according to the method similar to that in

5 Example 1 (7))

Elemental analysis for  $C_{23}H_{35}N_2O_4Cl$

Calculated: C, 62.93; H, 8.04; N, 6.38.

Found: C, 62.70; H, 8.29; N, 6.39.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.89 (9H, s), 0.99 (3H, t, J=7.3 Hz),  
10 1.48-1.60 (5H, m), 1.75-1.85 (2H, m), 2.20 (3H, s),  
3.83-4.05 (4H, m), 4.21 (2H, bs), 5.15 (2H, q, J=7.0 Hz),  
6.90 (1H, d, J=2.6 Hz), 7.18 (1H, dd, J=2.6, 8.8 Hz),  
8.19 (1H, d, J=8.8 Hz), 8.45 (3H, bs).

Example 106

15 3-Aminomethyl-6-bromo-2-isobutyl-4-phenyl-1(2H)-  
isoquinolinone

(1) To a solution of 4-bromophthalic anhydride (50 g,  
220 mmol) in benzene (500 mL) was added aluminum  
chloride (60 g, 450 mmol) by small portions under ice-  
20 cooling. The obtained mixture was stirred at room  
temperature for 24 h. The reaction mixture was poured  
into ice water and extracted with a mixed solvent of  
ethyl acetate - tetrahydrofuran (1/1). The extract was  
washed with brine, dried over anhydrous magnesium  
25 sulfate and concentrated under reduced pressure. The  
residue was purified by silica gel column chromatography  
and recrystallized from ethyl acetate - diisopropyl  
ether. The precipitated crystals were collected by  
filtration to give 2-benzoyl-4-bromobenzoic acid (33 g,  
30 49%) as crystals.

Melting point 185-187°C.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 7.36-7.73 (7H, m), 7.94 (1H, d, J=8.4 Hz).

(2) A mixture of 2-benzoyl-4-bromobenzoic acid (25 g, 82  
mmol), potassium carbonate (12 g, 87 mmol), diethyl  
35 bromomalonate (22 g, 92 mmol), acetone (450 mL) and N,N-  
dimethylformamide (8 mL) was stirred at room temperature



for 15 h. The solvent was evaporated under reduced pressure. The residue was poured into water and extracted with ethyl acetate. The residue was crystallized from hexane and the crystals were collected  
5 by filtration. The obtained crystals were added to a mixture of acetic acid (235 mL) and concentrated hydrochloric acid (360 mL) and the mixture was stirred at 120°C for 8 h. The reaction mixture was cooled and concentrated. The residue was poured into water and  
10 extracted with ethyl acetate. The extract was washed with brine, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The precipitated crystals were collected by filtration, washed with diisopropyl ether and dried to give 6-bromo-4-phenyl-1H-  
15 isochromene-3-carboxylic acid (17 g, 60%) as crystals. Melting point 205-206°C.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 7.20-7.28 (3H, m), 7.47-7.55 (3H, m), 7.77 (1H, dd, J=8.6, 1.8 Hz), 8.26 (1H, d, J=8.6 Hz).  
(3) A solution of 6-bromo-4-phenyl-1H-isochromene-3-  
20 carboxylic acid (8.0 g, 23 mmol) and isobutylamine (23 mL, 230 mmol) in methanol (120 mL) was stirred at room temperature for 15 h. The solvent was evaporated under reduced pressure, and the residue was acidified with concentrated hydrochloric acid and extracted with ethyl  
25 acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. To the residue was added a solution of 4N hydrogen chloride in ethyl acetate (150 mL) and the mixture was stirred at room temperature for 3 h.  
30 The solvent was evaporated under reduced pressure, and the precipitated crystals were collected by filtration with water. The crystals were washed with water and dried to give 6-bromo-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-3-carboxylic acid (8.1 g, 87%) as  
35 crystals. Melting point 233-235°C.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.92 (6H, d,  $J=6.6$  Hz), 2.21 (1H, m), 3.99 (2H, d,  $J=7.6\text{Hz}$ ), 7.32-7.38 (3H, m), 7.42-7.47 (3H, m), 7.60 (1H, dd,  $J=8.4, 2.0\text{Hz}$ ), 8.26 (1H, d,  $J=8.4\text{Hz}$ ).

(4) 6-Bromo-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-3-carboxylic acid (12.3 g, 30.7 mmol) was dissolved in tetrahydrofuran (100 mL), and oxalyl chloride (3.2 mL, 36.8 mmol) and *N,N*-dimethylformamide (5 drops) were added thereto. The mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (50 mL). The obtained solution was added dropwise to a suspension of sodium tetrahydroborate (4.0 g, 107 mmol) in 1,2-dimethoxyethane (50 mL) at 0°C. The obtained mixture was stirred at 0°C for 1 h. The reaction mixture was poured into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from diethyl ether - *n*-hexane to give 6-bromo-3-hydroxymethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (10.7 g; 90%) as crystals.

Melting point 176-177°C.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.97 (6H, d,  $J=6.6\text{Hz}$ ), 2.22 (1H, m), 2.35 (1H, t,  $J=5.8\text{Hz}$ ), 4.21 (2H, d,  $J=7.6\text{Hz}$ ), 4.44 (2H, d,  $J=5.8\text{Hz}$ ), 7.10 (1H, d,  $J=1.8\text{Hz}$ ), 7.30-7.35 (2H, m), 7.47 (1H, dd,  $J=8.4, 1.8\text{Hz}$ ), 7.50-7.56 (3H, m), 8.20 (1H, d,  $J=8.4\text{Hz}$ ).

(5) To a solution of 6-bromo-3-hydroxymethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (8.7 g, 22.5 mmol) and pyridine (5 drops) in tetrahydrofuran (30 mL) and toluene (30 mL) was added thionyl chloride (3.4 mL, 47.3 mmol). The obtained mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated, poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over

anhydrous magnesium sulfate and concentrated under reduced pressure to give 6-bromo-3-chloromethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (8.2 g, 90%) as crystals.

<sup>5</sup> Melting point 145-146°C.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:1.01 (6H, d, J=6.6Hz), 2.22 (1H, m), 4.17 (2H, d, J=7.6Hz), 4.37(2H, s), 7.14 (1H, d, J=1.8Hz), 7.31-7.37 (2H, m), 7.49-7.55 (3H, m), 7.59 (1H, dd, J=8.4, 1.8Hz), 8.34 (1H, d, J=8.4Hz).

<sup>10</sup> (7) A solution of 6-bromo-3-chloromethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (10 g, 24.7 mmol) in tetrahydrofuran (20 mL) and a solution of 2M ammonia in ethanol (200 mL) were sealed in a stainless tube and stirred at 140°C for 5 h. The reaction mixture was  
<sup>15</sup> cooled and concentrated. The residue was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was crystallized from diethyl ether and the  
<sup>20</sup> precipitated crystals were collected by filtration to give 3-aminomethyl-6-bromo-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (5.6 g, 53%) as crystals.

Melting point 129-130°C

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ:1.00 (6H, d, J = 6.6 Hz), 1.33 (2H, br),  
<sup>25</sup> 2.12-2.38 (1H, m), 3.65 (2H, s), 4.20 (2H, d, J = 7.8 Hz), 7.08 (1H, d, J = 1.6 Hz), 7.21-7.35 (2H, m), 7.42-7.60 (4H, m), 8.32 (1H, d, J = 9.0 Hz).

Elemental analysis for C<sub>20</sub>H<sub>21</sub>BrN<sub>2</sub>O

Calculated: C, 62.35; H, 5.49; N, 7.27.

<sup>30</sup> Found: C, 62.36; H, 5.64; N, 7.44.

#### Example 107

Methyl 3-aminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxylate hydrochloride

(1) To a solution of 3-aminomethyl-6-bromo-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (synthesized according to  
<sup>35</sup> the method similar to that in Example 106 (7)) (5.6 g,

14.5 mmol) and 4-dimethylaminopyridine (20 mg) in tetrahydrofuran (50 mL) was added di-t-butyl dicarbonate (6.3 g, 2.9 mmol). The obtained mixture was stirred at room temperature for 1 h. The reaction mixture was  
5 poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was crystallized from diethyl ether to give 3-tert-butoxycarbonylaminomethyl-6-bromo-  
10 2-isobutyl-4-phenyl-1(2H)-isoquinolinone (6.6 g, 94%) as crystals.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:1.00 (6H, d, J=7.0 Hz), 1.43 (9H, s), 2.23 (1H, m), 4.06 (2H, d, J=7.8 Hz), 4.19 (2H, d, J=5.4 Hz), 4.50 (1H, bs), 7.08 (1H, d, J=2.0Hz), 7.21-7.25 (2H,  
15 m), 7.48-7.56 (4H, m), 8.30 (1H, d, J=8.8Hz).

(2) A mixture of 3-tert-butoxycarbonylaminomethyl-6-bromo-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (3.0 g, 6.2 mmol), 1,3-bis(diphenylphosphino)propane (0.45 g, 1.1 mmol) and triethylamine (0.69 g, 6.8 mmol) in  
20 dimethyl sulfoxide (30 ml) and methanol (15 ml) was stirred under a carbon monoxide atmosphere at room temperature for 30 min. Palladium acetate (0.25 g, 1.1 mmol) was added to the resulting mixture and the mixture was stirred under a carbon monoxide atmosphere with  
25 heating at 80°C for 15 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by  
30 silica gel column chromatography to give methyl 3-tert-butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxylate (1.92 g, 83.5%) as crystals. Melting point 205-206°C.

Elemental analysis for C<sub>27</sub>H<sub>32</sub>N<sub>2</sub>O<sub>5</sub>

35 Calculated: C, 69.81; H, 6.94; N, 6.03.

Found: C, 69.71; H, 6.80; N, 6.13.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:1.01 (6H, d, J=6.6 Hz), 1.43 (9H, s), 2.26 (1H, m), 3.85 (3H, s), 4.09 (2H, d, J=7.6 Hz), 4.22 (2H, d, J=5.6 Hz), 4.47 (1H, bs), 7.23-7.28 (2H, m), 7.49-7.56 (3H, m), 7.66 (1H, d, J=1.0Hz), 8.05 (1H, dd, J=1.7, 8.0 Hz), 8.52 (1H, d, J=8.0 Hz).

(3) To a solution of methyl 3-tert-butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxylate (0.2 g, 0.43 mmol) in tetrahydrofuran (10 mL) was added a solution of 10% hydrogen chloride in methanol (20 mL). The obtained solution was stirred at room temperature for 15 h. The reaction mixture was concentrated under reduced pressure and the residue was crystallized from diethyl ether to give methyl 3-aminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxylate hydrochloride (0.17 g, 99%) as crystals.

Elemental analysis for C<sub>22</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub> HCl 1/4H<sub>2</sub>O

Calculated: C, 65.18; H, 6.34; N, 6.91.

Found: C, 65.08; H, 6.29; N, 6.86.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ:0.93 (6H, d, J=6.6 Hz), 2.12 (1H, m), 3.80 (3H, s), 3.89 (2H, s), 4.10 (2H, d, J=6.6 Hz), 7.42-7.46 (2H, m), 7.54 (1H, d, J=1.6 Hz), 7.54-7.62 (3H, m), 8.07 (1H, dd, J=8.4 Hz), 8.47 (1H, d, J=8.4 Hz), 8.58 (3H, s).

#### Example 108

3-Aminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxylic acid hydrochloride

(1) To a solution of methyl 3-tert-butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxylate (synthesized according to the method similar to that in Example 107 (2)) (0.28 g, 0.6 mmol) in tetrahydrofuran (10 ml) and methanol (10 ml) was added 1N sodium hydroxide (5 ml). The obtained mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate.

The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diethyl ether to give 3-tert-butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxylic acid (1.54 g, 98.7%) as crystals.

Elemental analysis for  $C_{26}H_{30}N_2O_5$

Calculated: C, 69.31; H, 6.71; N, 6.22.

10 Found: C, 69.17; H, 6.59; N, 6.27.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.96 (6H, d,  $J=6.6$  Hz), 1.07 (3H, t,  $J=7.4$  Hz), 1.49 (9H, s), 1.50-1.72 (2H, m), 1.84-1.98 (2H, m), 2.14-2.21 (1H, m), 3.90 (2H, t,  $J=6.4$  Hz), 4.00 (2H, d,  $J=6.8$  Hz), 4.55 (2H, d,  $J=5.0$  Hz), 5.37 (1H, bs), 8.08-8.13 (1H, m), 8.35-8.46 (2H, m).

(2) To a solution of 3-tert-butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxylic acid (0.15 g, 0.33 mmol) in tetrahydrofuran (6 mL) was added a solution of 4N hydrogen chloride in dioxane (10 mL).

20 The obtained solution was stirred at room temperature for 15 h. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from diethyl ether to give 3-aminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxylic acid hydrochloride (0.09 g, 69%) as crystals.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.89 (6H, d,  $J=6.6$  Hz), 1.01 (3H, t,  $J=7.4$  Hz), 1.50-1.69 (2H, m), 1.80-1.93 (2H, m), 1.99-2.12 (1H, m), 3.97 (2H, t,  $J=6.4$  Hz), 3.99 (2H, d,  $J=7.6$  Hz), 4.21 (2H, s), 8.09 (1H, dd,  $J=1.4, 8.4$  Hz), 8.34 (1H, d,  $J=1.4$  Hz), 8.38 (1H, d,  $J=8.4$  Hz), 8.69 (3H, bs).

#### Example 109

3-Aminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxamide hydrochloride [3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxamide hydrochloride]

30 (1) A solution of 3-tert-butoxycarbonylaminomethyl-2-

isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxylic acid (synthesized according to the method similar to that in Example 108 (1)) (0.6 g, 1.3 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.5 g, 2.6 mmol) and 1-hydroxybenzotriazole ammonium salt (0.4 g, 2.6 mmol) in N,N-dimethylformamide (3 ml) was stirred at room temperature for 3 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed successively with saturated aqueous sodium hydrogencarbonate solution and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was crystallized from diethyl ether - n-hexane to give 3-tert-butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxamide (0.5 g, 86%) as crystals.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.00 (6H, d, J=6.6 Hz), 1.43 (9H, s), 2.24 (1H, m), 4.08 (2H, d, J=7.2 Hz), 4.20 (2H, d, J=5.4 Hz), 4.68 (1H, bs), 5.73 (1H, bs), 6.08 (1H, bs), 7.24-7.29 (2H, m), 7.38 (1H, d, J=2.0 Hz), 7.47-7.56 (3H, m), 7.74 (1H, dd, J=8.8, 2.0 Hz), 8.45 (1H, d, J=8.8 Hz).

(2) To a solution of 3-tert-butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxamide (0.15 g, 0.33 mmol) in tetrahydrofuran (6 mL) was added a solution of 4N hydrogen chloride in dioxane (10 mL). The obtained solution was stirred at room temperature for 6 h. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from diethyl ether to give 3-aminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxamide hydrochloride (0.11 g, 85%) as crystals.

Melting point 240-242°C.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.92 (6H, d, J=6.6 Hz), 2.11 (1H, m), 3.87 (2H, d, J=5.6 Hz), 4.10 (2H, d, J=7.2 Hz), 7.39 (1H, d, 1.4 Hz), 7.40-7.43 (2H, m), 7.56-7.62 (4H, m), 8.00 (1H, dd, J=8.4, 1.4 Hz), 8.16 (1H, s), 8.37 (1H, d, J=8.4 Hz), 8.61 (3H, bs).

**Example 110**

3-Aminomethyl-6-benzyloxycarbonylamino-2-isobutyl-4-phenyl-1(2H)-isoquinolinone hydrochloride

- (1) A solution of 3-tert-butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxylic acid (synthesized according to the method similar to that in Example 108 (1)) (0.5 g, 1.1 mmol), diphenylphosphoryl azide (0.28 ml, 1.3 mmol) and triethylamine (0.18 ml, 1.3 mmol) in N,N-dimethylformamide (5 ml) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in toluene (20 ml) and the mixture was stirred with heating at 100°C for 2 h. To the obtained mixture was added benzyl alcohol (0.14 ml, 1.3 mmol) and the mixture was stirred with heating at 100°C for 1 h. The reaction mixture was cooled, poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was crystallized from diisopropyl ether to give 6-benzyloxycarbonylamino-3-tert-butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (0.47 g, 77%) as crystals.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.99 (6H, d, J=6.6 Hz), 1.42 (9H, s), 2.23 (1H, m), 4.05 (2H, d, J=7.6Hz), 4.18 (2H, d, J=5.2 Hz), 4.47 (1H, bs), 5.13 (2H, s), 6.75 (1H, d, J=1.8Hz), 6.76 (1H, s), 7.21-7.26 (2H, m), 7.34-7.75 (5H, m), 7.45-7.56 (3H, m), 7.65 (1H, dd, J=8.8, 1.8Hz), 8.41 (1H, d, J=8.8Hz).

- (2) To a solution of 6-benzyloxycarbonylamino-3-tert-butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (0.07 g, 0.13 mmol) in tetrahydrofuran (2 mL) was added a solution of 4N hydrogen chloride in ethyl acetate (10 mL). The obtained solution was



stirred at room temperature for 5 h. The reaction mixture was concentrated under reduced pressure and the residue was crystallized from diethyl ether to give 3-aminomethyl-6-benzyloxycarbonylamino-2-isobutyl-4-

5 phenyl-1(2H)-isoquinolinone hydrochloride (0.05 g, 81%) as crystals.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ:0.91 (6H, d, J=6.6 Hz), 2.08 (1H, m), 3.84 (2H, s), 4.03 (2H, d, J=7.4 Hz), 5.08 (2H, s), 7.22 (1H, d, J=1.8 Hz), 7.35-7.37 (7H, s), 7.54-7.58 (2H, m),  
10 7.64 (1H, dd, J=8.8, 1.8Hz), 8.24 (1H, d, J=8.8 Hz), 8.44 (3H, s), 10.16 (1H, s).

#### Example 111

6-Amino-3-aminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone dihydrochloride

15 (1) To a mixed solution of 6-benzyloxycarbonylamino-3-tert-butoxycarbonylamino-methyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 110. (1)) (0.45 g, 0.81 mmol) in tetrahydrofuran (20 ml) and ethanol (20 ml) was  
20 added 5% palladium-carbon (0.1 g). The obtained mixture was hydrogenated at ambient temperature and atmospheric pressure. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The precipitated crystals were collected by filtration to  
25 give 6-amino-3-tert-butoxycarbonylamino-methyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (0.31 g, 87.0%) as crystals.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.99 (6H, d, J=6.8 Hz), 1.42 (9H, s), 2.22 (1H, m), 3.94 (2H, bs), 4.02 (2H, d, J=7.4Hz), 4.15  
30 (2H, d, J=5.4Hz), 4.40 (1H, bs), 6.12 (1H, d, J=2.2Hz), 6.78 (1H, dd, J=8.8, 2, 2Hz), 7.21-7.26 (2H, m), 7.44-7.53 (3H, m), 8.27 (1H, d, J=8.8Hz).

(2) 6-Amino-3-aminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone dihydrochloride was synthesized from 6-amino-3-tert-butoxycarbonylamino-methyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone according to the method  
35

similar to that in Example 110 (2).

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ:0.90 (6H, d, J=6.6 Hz), 2.05 (1H, m), 3.76 (2H, bs), 3.99 (2H, d, J=6.6Hz), 5.44 (3H, bs), 6.00 (1H, d, J=2.0Hz), 6.84 (1H, dd, t, J=8.8, 2.0Hz),  
5 7.34-7.38 (2H, m), 7.50-7.59 (3H, m), 8.03 (1H, d, J=8.8 Hz), 8.48 (3H, bs).

#### Example 112

6-Acetylamino-3-aminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone hydrochloride

10 (1) A mixture of 6-amino-3-tert-butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 111 (1)) (0.1 g, 0.24 mmol), acetyl chloride (38 mg, 0.48 mmol), sodium  
15 hydrogencarbonate (81 mg, 0.96 mmol), water (0.5 ml) and ethyl acetate (5 ml) was stirred at room temperature for 2 h. The reaction mixture was extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under  
20 reduced pressure. The residue was crystallized from diisopropyl ether to give 6-acetylamino-3-tert-butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (80 mg, 73%) as crystals.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.87 (6H, d, J=7.0 Hz), 1.42 (9H, s),  
25 2.10 (3H, s), 2.23 (1H, m), 4.05 (2H, d, J=7.4Hz), 4.19 (2H, d, J=5.6Hz), 4.60 (1H, bs), 6.95 (1H, s), 7.24-7.28 (2H, m), 7.37 (1H, s), 7.47-7.55 (3H, m), 7.69 (1H, d, J=8.8Hz), 8.37 (1H, d, J=8.8Hz).

(2) 6-Acetylamino-3-aminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone hydrochloride was synthesized from  
30 6-acetylamino-3-tert-butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone according to the method similar to that in Example 110 (2).

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ:0.91 (6H, d, J=6.6 Hz), 1.98 (3H, s),  
35 2.08 (1H, m), 3.84 (2H, s), 4.03 (2H, d, J=7.0Hz), 7.19 (1H, d, J=1.8Hz), 7.35-7.39 (2H, m), 7.49-7.58 (3H, m),

7.86 (1H, dd, J=8.8, 1.8Hz), 8.25 (1H, d, J=8.8Hz), 8.45 (3H, bs), 10.28 (1H, s).

The compounds of the following Examples 113 to 130 were synthesized according to the method similar to that in Example 106.

**Example 113**

3-(Aminomethyl)-6-chloro-2-ethyl-4-phenyl-1(2H)-isoquinolinone

Melting point 126-127°C

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.39 (2H, br), 1.42 (3H, t, J = 7.0 Hz), 3.64 (2H, s), 4.43 (2H, q, J = 7.0 Hz), 6.91 (1H, d, J = 2.2 Hz), 7.23-7.31 (2H, m), 7.38 (1H, dd, J = 2.2 and 8.4 Hz), 7.45-7.57 (3H, m), 8.41 (1H, d, J = 8.4 Hz).

Elemental analysis for C<sub>18</sub>H<sub>17</sub>ClN<sub>2</sub>O·0.125H<sub>2</sub>O

Calculated: C, 68.62; H, 5.51; N, 8.89.

Found: C, 68.61; H, 5.40; N, 8.84.

**Example 114**

3-(Aminomethyl)-6-chloro-4-phenyl-2-propyl-1(2H)-isoquinolinone

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.04 (3H, t, J = 7.4 Hz), 1.17 (2H, br), 1.71-1.93 (2H, m), 3.63 (2H, s), 4.28 (2H, t, J = 7.6 Hz), 6.90 (1H, d, J = 2.2 Hz), 7.21-7.32 (2H, m), 7.37 (1H, dd, J = 2.2 and 8.4 Hz), 7.41-7.58 (3H, m), 8.40 (1H, d, J = 8.4 Hz).

Elemental analysis for C<sub>19</sub>H<sub>19</sub>ClN<sub>2</sub>O

Calculated: C, 69.83; H, 5.86; N, 8.57.

Found: C, 69.97; H, 5.90; N, 8.49.

**Example 115**

3-(Aminomethyl)-2-butyl-6-chloro-4-phenyl-1(2H)-isoquinolinone

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.00 (3H, t, J = 7.4 Hz), 1.23 (2H, br), 1.38-1.60 (2H, m), 1.68-1.84 (2H, m), 3.63 (2H, s), 4.33 (2H, t, J = 7.6 Hz), 6.90 (1H, d, J = 2.0 Hz), 7.22-7.31 (2H, m), 7.38 (1H, dd, J = 2.0 and 8.8 Hz), 7.45-7.58 (3H, m), 8.41 (1H, d, J = 8.8 Hz).

Elemental analysis for C<sub>20</sub>H<sub>21</sub>ClN<sub>2</sub>O

Calculated: C, 70.48; H, 6.21; N, 8.22.

Found: C, 70.27; H, 6.18; N, 8.09.

**Example 116**

3-(Aminomethyl)-6-bromo-2-methyl-4-phenyl-1(2H)-

5 isoquinolinone

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.30 (2H, br), 3.66 (2H, s), 3.84 (3H, s), 7.10 (1H, d, J = 2.0 Hz), 7.20-7.32 (2H, m), 7.45-7.59 (4H, m), 8.33 (1H, d, J = 8.8 Hz).

Elemental analysis for C<sub>17</sub>H<sub>15</sub>BrN<sub>2</sub>O

10 Calculated: C, 59.49; H, 4.41; N, 8.16.

Found: C, 59.61; H, 4.65; N, 7.78.

**Example 117**

3-(Aminomethyl)-6-chloro-2-pentyl-4-phenyl-1(2H)-

isoquinolinone

15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.93 (3H, t, J = 7.4 Hz), 1.20-1.53 (6H, m), 1.70-1.90 (2H, m), 3.63 (2H, s), 4.31 (2H, t, J = 8.0 Hz), 6.90 (1H, d, J = 2.2 Hz), 7.22-7.31 (2H, m), 7.37 (1H, dd, J = 2.2 and 8.4 Hz), 7.45-7.58 (3H, m), 8.40 (1H, d, J = 8.4 Hz).

20 Elemental analysis for C<sub>21</sub>H<sub>23</sub>ClN<sub>2</sub>O

Calculated: C, 71.07; H, 6.53; N, 7.89.

Found: C, 70.82; H, 6.34; N, 7.72.

**Example 118**

3-(Aminomethyl)-6-chloro-2-isobutyl-4-phenyl-1(2H)-

25 isoquinolinone

Melting point 123-124°C

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.00 (6H, d, J = 6.6 Hz), 1.18 (2H, br), 2.12-2.38 (1H, m), 3.66 (2H, s), 4.20 (2H, d, J = 7.4 Hz), 6.90 (1H, d, J = 1.6 Hz), 7.21-7.31 (2H, m), 7.37 (1H, dd, J = 1.6 and 8.4 Hz), 7.45-7.58 (3H, m), 8.40 (1H, d, J = 8.4 Hz).

30 Elemental analysis for C<sub>20</sub>H<sub>21</sub>ClN<sub>2</sub>O

Calculated: C, 70.48; H, 6.21; N, 8.22.

Found: C, 70.35; H, 6.07; N, 8.10.

35 **Example 119**

3-(Aminomethyl)-6-chloro-2-(cyclohexylmethyl)-4-phenyl-

**1(2H)-isoquinolinone**

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.00-1.47 (8H, m), 1.56-2.00 (5H, m),  
3.66 (2H, s), 4.21 (2H, d, J = 6.8 Hz), 6.90 (1H, d, J =  
2.0 Hz), 7.22-7.32 (2H, m), 7.37 (1H, dd, J = 2.0 and  
5 8.8 Hz), 7.47-7.58 (3H, m), 8.40 (1H, d, J = 8.8 Hz).

Elemental analysis for C<sub>23</sub>H<sub>25</sub>ClN<sub>2</sub>O

Calculated: C, 72.52; H, 6.62; N, 7.35.

Found: C, 72.34; H, 6.76; N, 7.21.

**Example 120**

10 3-(Aminomethyl)-6,7-dichloro-4-(4-fluorophenyl)-2-  
isobutyl-1(2H)-isoquinolinone hydrochloride

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, free base) δ: 0.99 (6H, d, J = 6.8 Hz),  
1.36 (2H, br), 2.10-2.35 (1H, m), 3.65 (2H, s), 4.20 (2H,  
d, J = 7.6 Hz), 6.99 (1H, s), 7.24 (4H, d, J = 7.4 Hz),  
15 8.53 (1H, s).

Elemental analysis for C<sub>20</sub>H<sub>19</sub>Cl<sub>2</sub>N<sub>2</sub>OF·HCl·H<sub>2</sub>O

Calculated: C, 53.65; H, 4.95; N, 6.26.

Found: C, 53.69; H, 4.84; N, 5.96.

**Example 121**

20 3-(Aminomethyl)-6,7-dichloro-2-isobutyl-4-phenyl-1(2H)-  
isoquinolinone

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.00 (6H, d, J = 7.0 Hz), 1.13 (2H, br),  
2.10-2.36 (1H, m), 3.65 (2H, s), 4.20 (2H, d, J = 7.4  
Hz), 7.02 (1H, s), 7.20-7.32 (2H, m), 7.45-7.59 (3H, m),  
25 8.54 (1H, s).

Elemental analysis for C<sub>20</sub>H<sub>20</sub>Cl<sub>2</sub>N<sub>2</sub>O

Calculated: C, 64.01; H, 5.37; N, 7.46.

Found: C, 63.71; H, 5.39; N, 7.23.

**Example 122**

30 3-(Aminomethyl)-6-chloro-2-neopentyl-4-phenyl-1(2H)-  
isoquinolinone

Melting point 173-174°C

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.02 (9H, s), 1.23 (2H, br), 3.71 (2H,  
s), 4.30 (2H, br), 6.90 (1H, d, J = 2.2 Hz), 7.20-7.30  
35 (2H, m), 7.37 (1H, dd, J = 2.2 and 8.4 Hz), 7.42-7.68  
(3H, m), 8.39 (1H, d, J = 8.4 Hz).

Elemental analysis for  $C_{21}H_{23}ClN_2O$

Calculated: C, 71.07; H, 6.53; N, 7.89.

Found: C, 70.89; H, 6.54; N, 7.61.

**Example 123**

5 3-(Aminomethyl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone

Melting point 129-130°C

$^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 1.01 (6H, d,  $J = 7.0$  Hz), 1.23 (2H, br),  
2.17-2.40 (1H, m), 3.68 (2H, s), 4.22 (2H, d,  $J = 7.8$   
Hz), 6.90-7.00 (1H, m), 7.23-7.34 (2H, m), 7.38-7.57 (5H,  
10 m), 8.44-8.52 (1H, m).

Elemental analysis for  $C_{20}H_{22}N_2O$

Calculated: C, 78.40; H, 7.24; N, 9.14.

Found: C, 78.30; H, 7.50; N, 9.06.

**Example 124**

15 3-(Aminomethyl)-4-(4-chlorophenyl)-2-isobutyl-1(2H)-  
isoquinolinone

Melting point 119-120°C

$^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 1.00 (6H, d,  $J = 6.6$  Hz), 1.15 (1H, br),  
1.61 (1H, br), 2.14-2.39 (1H, m), 3.67 (2H, s), 4.21 (2H,  
20 d,  $J = 7.8$  Hz), 6.88-6.97 (1H, m), 7.20-7.29 (2H, m),  
7.40-7.56 (4H, m), 8.43-8.52 (1H, m).

Elemental analysis for  $C_{20}H_{21}ClN_2O$

Calculated: C, 70.48; H, 6.21; N, 8.22.

Found: C, 70.36; H, 6.40; N, 8.19.

25 **Example 125**

3-(Aminomethyl)-4-(4-methylphenyl)-2-isobutyl-1(2H)-  
isoquinolinone hydrochloride

Melting point 178-180°C (dec.)

$^1H$ -NMR ( $CDCl_3$ , free base)  $\delta$ : 1.00 (6H, d,  $J = 6.6$  Hz),  
30 1.48 (2H, br), 2.18-2.37 (1H, m), 2.46 (3H, s), 3.69 (2H,  
s), 4.22 (2H, d,  $J = 7.8$  Hz), 6.95-7.04 (1H, m), 7.17  
(2H, d,  $J = 8.0$  Hz), 7.31 (2H, d,  $J = 7.0$  Hz), 7.37-7.53  
(2H, m), 8.43-8.53 (1H, m).

Elemental analysis for  $C_{21}H_{24}N_2O \cdot HCl \cdot 0.5H_2O$

35 Calculated: C, 68.93; H, 7.16; N, 7.66.

Found: C, 69.25; H, 7.11; N, 7.30.

**Example 126**

3-(Aminomethyl)-6-fluoro-2-isobutyl-4-phenyl-1(2H)-isoquinolinone

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.00 (6H, d, J = 6.6 Hz), 1.12 (2H, br),  
5 2.15-2.38 (1H, m), 3.67 (2H, s), 4.20 (2H, d, J = 7.4 Hz), 6.56 (1H, dd, J = 2.6 and 10.6 Hz), 7.13 (1H, dt, J = 2.6 and 8.8 Hz), 7.23-7.33 (2H, m), 7.41-7.57 (3H, m), 8.48 (1H, dd, J = 5.8 and 8.8 Hz).

Elemental analysis for C<sub>20</sub>H<sub>21</sub>FN<sub>2</sub>O·0.25H<sub>2</sub>O

10 Calculated: C, 73.04; H, 6.59; N, 8.52.

Found: C, 73.32; H, 6.72; N, 8.43.

**Example 127**

3-(Aminomethyl)-2-isobutyl-6-methoxy-4-phenyl-1(2H)-isoquinolinone

15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.00 (6H, d, J = 6.6 Hz), 1.26 (2H, br), 2.15-2.38 (1H, m), 3.65 (2H, s), 3.67 (3H, s), 4.18 (2H, d, J = 7.2 Hz), 6.30 (1H, d, J = 2.4 Hz), 7.02 (1H, dd, J = 2.4 and 8.8 Hz), 7.23-7.34 (2H, m), 7.39-7.57 (3H, m), 8.41 (1H, d, J = 8.8 Hz).

20 Elemental analysis for C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>

Calculated: C, 74.97; H, 7.19; N, 8.33.

Found: C, 74.73; H, 7.40; N, 8.32.

**Example 128**

3-(Aminomethyl)-6-ethoxy-2-isobutyl-4-phenyl-1(2H)-isoquinolinone

25 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.00 (6H, d, J = 7.0 Hz), 1.21 (2H, br), 1.33 (3H, t, J = 7.0 Hz), 2.13-2.38 (1H, m), 3.65 (2H, s), 3.88 (2H, q, J = 7.0 Hz), 4.18 (2H, d, J = 7.4 Hz), 6.29 (1H, d, J = 2.6 Hz), 7.01 (1H, dd, J = 2.6 and 8.8 Hz),  
30 7.22-7.32 (2H, m), 7.41-7.55 (3H, m), 8.39 (1H, d, J = 8.8 Hz).

Elemental analysis for C<sub>22</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>

Calculated: C, 75.40; H, 7.48; N, 7.99.

Found: C, 75.43; H, 7.69; N, 8.17.

**Example 129**

3-(Aminomethyl)-2-isobutyl-4-phenyl-6-propoxy-1(2H)-

## isoquinolinone

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.95 (3H, t, J = 7.4Hz), 0.99 (6H, d, J = 7.0 Hz), 1.32 (2H, br), 1.61-1.82 (2H, m), 2.13-2.38 (1H, m), 3.64 (2H, s), 3.77 (2H, t, J = 6.6Hz), 4.18 (2H, d, J = 7.4 Hz), 6.28 (1H, d, J = 2.6 Hz), 7.01 (1H, dd, J = 2.6 and 9.2 Hz), 7.22-7.31 (2H, m), 7.42-7.56 (3H, m), 8.39 (1H, d, J = 9.2 Hz).

Elemental analysis for C<sub>23</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>

Calculated: C, 75.79; H, 7.74; N, 7.69.

10 Found: C, 75.81; H, 7.45; N, 7.56.

## Example 130

3-(Aminomethyl)-2-isobutyl-6,7-dimethoxy-4-phenyl-1(2H)-isoquinolinone

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.01 (6H, d, J = 6.6 Hz), 1.34 (2H, br), 2.15-2.40 (1H, m), 3.66 (5H, s), 4.01 (3H, s), 4.21 (2H, d, J = 7.4 Hz), 6.28 (1H, s), 7.25-7.35 (2H, m), 7.40-7.57 (3H, m), 7.87 (1H, s).

Elemental analysis for C<sub>22</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub>·0.5H<sub>2</sub>O

Calculated: C, 70.38; H, 7.25; N, 7.46.

20 Found: C, 70.56; H, 7.36; N, 7.39.

## Example 131

3-(Aminomethyl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carbonitrile hydrochloride.

(1) A solution of 3-tert-butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxamide (synthesized according to the method similar to that in Example 109 (1)) (0.3 g, 0.67 mmol) and cyanuric chloride (0.37 g, 2 mmol) in N,N-dimethylformamide (3 mL) was stirred at 0°C for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed successively with water, 10% aqueous citric acid solution, saturated aqueous sodium hydrogencarbonate solution and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give a amorphous solid of



tert-butyl (6-cyano-2-isobutyl-4-phenyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.28 g, 97%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.01 (6H, d, J=7.0 Hz), 1.43 (9H, s), 2.24 (1H, m), 4.09 (2H, d, J=7.0 Hz), 4.23 (2H, d, J=5.4 Hz), 4.43 (1H, bs), 7.21-7.29 (3H, m), 7.51-7.59 (3H, m), 7.65 (1H, dd, J=1.4, 8.0 Hz), 8.55 (1H, d, J=8.0 Hz).

(2) 3-(Aminomethyl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carbonitrile hydrochloride was synthesized from tert-butyl (6-cyano-2-isobutyl-4-phenyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate in the same manner as in Example 1 (7).

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.93 (6H, d, J=6.6 Hz), 2.11 (1H, m), 3.89 (2H, s), 4.11 (2H, d, J=7.4 Hz), 7.22 (1H, d, J=1.6 Hz), 7.42-7.46 (2H, m), 7.58-7.61 (3H, m), 7.97 (1H, dd, J=1.6, 8.4 Hz), 8.48 (1H, d, J=8.4 Hz), 8.67 (3H, bs).

#### Example 132

3-(Aminomethyl)-4-phenyl-6-(1-pyrrolidinylcarbonyl)-2-isobutyl-1(2H)-isoquinolinone hydrochloride

(1) A mixture of 3-tert-butoxycarbonylaminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxylic acid (synthesized according to the method similar to that in Example 108 (1)), (100 mg, 0.22 mmol), hydrochloric acid 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (63 mg, 0.33 mmol), 1-hydroxy-7-azabenzotriazole (30 mg, 0.22 mmol), pyrrolidine (31 mg, 0.44 mmol) and N,N-dimethylformamide (3 mL) was stirred at room temperature for 3 h. The reaction mixture was poured into 10% aqueous citric acid solution and extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 3-(tert-butoxycarbonylaminomethyl)-2-isobutyl-4-phenyl-6-(1-pyrrolidinylcarbonyl)-1(2H)-isoquinolinone (70 mg, 64%) as an amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.01 (6H, d, J=6.6 Hz), 1.43 (9H, s),

1.79-1.99 (4H, m), 2.25 (1H, m), 3.21 (2H, t, J=6.2 Hz),  
3.57 (2H, t, J=6.8Hz), 4.09 (2H, d, J=7.6 Hz), 4.21 (2H,  
d, J=6.0Hz), 4.44 (1H, bs), 7.08 (1H, d, J=1.6Hz), 7.21-  
7.27 (2H, m), 7.45-7.51 (3H, m), 7.56 (1H, dd, J=8.4,  
5 1.6Hz), 8.50 (1H, d, J=8.4Hz).

(2) 3-(Aminomethyl)-2-isobutyl-4-phenyl-6-(1-  
pyrrolidinylcarbonyl)-1(2H)-isoquinolinone hydrochloride  
was synthesized from 3-(tert-butoxycarbonylaminomethyl)-  
2-isobutyl-4-phenyl-6-(1-pyrrolidinylcarbonyl)-1(2H)-  
10 isoquinolinone in the same manner as in Example 1 (7).

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.93 (6H, d, J=6.6 Hz), 1.70-1.90 (4H,  
m), 2.11 (1H, m), 3.20 (2H, t, J=6.4Hz), 3.90 (2H, t,  
J=6.2Hz), 3.88 (2H, s), 4.09 (2H, d, J=7.4Hz), 6.96 (1H,  
d, J=1.6Hz), 7.39-7.44 (2H, m), 7.56-7.64 (3H, m), 7.69  
15 (1H, dd, J=8.4, 1.6Hz), 8.37 (1H, d, J=8.4Hz), 8.55 (3H,  
bs).

The compounds of the following Examples 133 to 141  
were synthesized according to the method similar to that  
in Example 132.

20 **Example 133**

3-Aminomethyl-N-benzyl-2-isobutyl-4-phenyl-1(2H)-  
isoquinolinone-6-carboxamide hydrochloride

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.93 (6H, d, J=6.6 Hz), 2.11 (1H, m),  
3.88 (2H, s), 4.09 (2H, d, J=6.6Hz), 4.36 (2H d,  
25 J=6.0Hz), 7.22-7.34 (5H, m), 7.40-7.45 (3H, m), 7.57-  
7.60 (3H, m), 8.04 (1H, d, J=8.4Hz), 8.41 (1H, d,  
J=8.4Hz), 8.52 (3H, bs), 9.28 (1H, t, J=6.0Hz).

**Example 134**

3-Aminomethyl-2-isobutyl-N-methyl-4-phenyl-1(2H)-  
30 isoquinolinone-6-carboxamide hydrochloride

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.93 (6H, d, J=6.6 Hz), 2.11 (1H, m),  
2.72 (3H, d, J=4.8Hz), 3.87 (2H, s), 4.09 (2H, d,  
J=6.8Hz), 7.39-7.43 (3H, m), 7.54-7.60 (3H, m), 7.95 (1H,  
dd, J=8.6, 1.6Hz), 8.39 (1H, d, J=8.6Hz), 8.60 (3H, bs),  
35 8.64 (1H, t, J=4.8Hz).

**Example 135**

3-Aminomethyl-N-cyclopropyl-2-isobutyl-4-phenyl-1(2H)-  
isoquinolinone-6-carboxamide hydrochloride

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.49-0.59 (2H, m), 0.62-0.71 (2H, m),  
0.92 (6H, d, J=6.6 Hz), 2.11 (1H, m), 2.73 (1H, m), 3.88  
5 (2H, s), 4.08 (2H, d, J=7.0Hz), 7.39 (1H, d, J=1.4Hz),  
7.40-7.43 (2H, m), 7.58-7.61 (3H, m), 7.94 (1H, dd,  
J=8.4, 1.4Hz), 8.37 (1H, d, J=8.4Hz), 8.46 (3H, bs),  
8.66 (1H, t, J=4.0Hz).

**Example 136**

10 3-Aminomethyl-2-isobutyl-4-phenyl-N-propyl-1(2H)-  
isoquinolinone-6-carboxamide hydrochloride

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.83 (3H, t, J=7.4Hz), 0.92 (6H, d,  
J=6.6 Hz), 1.40-1.60 (2H, m), 2.11 (1H, m), 3.15 (2H, m),  
3.88 (2H, s), 4.08 (2H, d, J=7.0Hz), 7.39 (1H, d,  
15 J=1.6Hz), 7.39-7.43 (2H, m), 7.57-7.60 (3H, m), 7.97 (1H,  
dd, J=8.4, 1.6Hz), 8.39 (1H, d, J=8.4Hz), 8.45 (3H, bs),  
8.66 (1H, t, J=4.8Hz).

**Example 137**

20 3-Aminomethyl-N-ethyl-2-isobutyl-4-phenyl-1(2H)-  
isoquinolinone-6-carboxamide hydrochloride

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.92 (6H, d, J=6.6 Hz), 1.07 (3H, t,  
J=7.0), 2.11 (1H, m), 3.15-3.29 (2H, m), 3.87 (2H, s),  
4.08 (2H, d, J=7.0Hz), 7.38-7.43 (3H, m), 7.55-7.63 (3H,  
m), 7.97 (1H, dd, J=8.4, 1.8Hz), 8.38 (1H, d, J=8.4Hz),  
25 8.45 (3H, bs), 8.68 (1H, t, J=5.0Hz).

**Example 138**

3-Aminomethyl-N,N-dimethyl-2-isobutyl-4-phenyl-1(2H)-  
isoquinolinone-6-carboxamide hydrochloride

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.93 (6H, d, J=6.6 Hz), 2.11 (1H, m),  
30 2.78 (3H, s), 2.91 (3H, s), 3.88 (2H, s), 4.08 (2H, d,  
J=7.4Hz), 6.84 (1H, d, J=1.0Hz), 7.39-7.43 (2H, m),  
7.54-7.61 (4H, m), 8.37 (1H, d, J=8.6Hz), 8.50 (3H, bs).

**Example 139**

Ethyl N-[(3-aminomethyl-2-isobutyl-4-phenyl-1(2H)-  
35 isoquinolinone-6-yl)carbonyl]glycinate hydrochloride

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.93 (6H, d, J=6.6 Hz), 1.17 (3H, t,

J=7.2Hz), 2.11 (1H, m), 3.88 (2H, s), 3.94 (2H, d, J=5.6Hz), 4.08 (2H, q, J=7.2Hz), 4.08 (2H, d, J=7.0Hz), 7.39-7.43 (3H, m), 7.57-7.60 (3H, m), 8.00 (1H, dd, J=8.4, 1.6Hz), 8.43 (1H, d, J=8.4Hz), 8.43 (3H, bs),  
5 9.15 (1H, t, J=5.6Hz).

**Example 140**

3-(Aminomethyl)-6-[(4-hydroxypiperidin-1-yl)carbonyl]-2-isobutyl-4-phenyl-1(2H)-isoquinolinone hydrochloride

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.93 (6H, d, J=6.6 Hz), 1.20-1.80 (6H,  
10 m), 2.11 (1H, m), 2.90-3.30 (2H, m), 3.67 (1H, m), 3.89 (2H, s), 4.07 (2H, d, J=6.4Hz), 4.80 (1H, bs), 6.83 (1H, m), 7.40-7.43 (2H, m), 7.54-7.61 (4H, m), 8.38 (1H, d, J=8.4Hz), 8.46 (3H, bs).

**Example 141**

15 3-Aminomethyl-N-(2,2,2-trifluoroethyl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxamide hydrochloride

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.93 (6H, d, J=6.6 Hz), 2.12 (1H, m), 3.89 (2H, s), 4.00-4.10 (4H, m), 7.39-7.44 (3H, m), 7.57-7.61 (3H, m), 8.02 (1H, dd, J=8.6, 1.4Hz), 8.44 (1H,  
20 d, J=8.4Hz), 8.46 (3H, bs), 9.31 (1H, t, J=6.3Hz).

**Example 142**

3-Aminomethyl-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carboxamide hydrochloride

(1) To a solution of 4-bromophthalic anhydride (50 g,  
25 220 mmol) in fluorobenzene (300 mL) was added aluminum chloride (60 g, 450 mmol) by small portions under ice-cooling. The obtained mixture was stirred at room temperature for 15 h. The reaction mixture was poured into ice water and extracted with ethyl acetate. The  
30 extract was washed with 1N hydrochloric acid and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was crystallized from ethyl acetate-diisopropyl ether and the precipitated crystals were collected by filtration. The  
35 crystals were recrystallized from ethyl acetate to give a solid of a mixture (9:1)(7 g, 10%) of 2-(4-

fluorobenzoyl)-4-bromobenzoic acid and 2-(4-fluorobenzoyl)-5-bromobenzoic acid.

2-(4-fluorobenzoyl)-4-bromobenzoic acid:  $^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 7.06-7.17 (2H, m), 7.50 (1H, d,  $J=2.0\text{Hz}$ ), 7.69-7.79 (3H, m), 7.95 (1H, d,  $J=8.4\text{ Hz}$ ).

(2) A solid of 6-bromo-4-(4-fluorophenyl)-1H-isochromene-3-carboxylic acid (5.5 g, 69%) was obtained from 2-(4-fluorobenzoyl)-4-bromobenzoic acid (7 g, 22 mmol) in the same manner as in Example 106 (2).

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 7.21-7.27 (5H, m), 7.79 (1H, dd,  $J=8.4$ , 1.8 Hz), 8.27 (1H, d,  $J=8.6\text{ Hz}$ ).

(3) 6-Bromo-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-3-carboxylic acid (5.3 g, 85%) was obtained as crystals from 6-bromo-4-(4-fluorophenyl)-1H-isochromene-3-carboxylic acid (5.4 g, 14.9 mmol) in the same manner as in Example 106 (3).

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.94 (6H, d,  $J=7.0\text{ Hz}$ ), 2.28 (1H, m), 4.02 (2H, d,  $J=7.4\text{Hz}$ ), 7.12-7.25 (3H, m), 7.33-7.41 (2H, m), 7.61 (1H, dd,  $J=8.4$ , 1.8Hz), 8.34 (1H, d,  $J=8.4\text{Hz}$ ).

(4) 6-Bromo-4-(4-fluorophenyl)-3-hydroxymethyl-2-isobutyl-1(2H)-isoquinolinone (4.9 g, 96%) was obtained as crystals from 6-bromo-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-3-carboxylic acid (5.3 g, 12.6 mmol) in the same manner as in Example 106 (4).

Melting point 194-196°C.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.98 (6H, d,  $J=7.0\text{Hz}$ ), 1.94 (1H, t,  $J=6.0\text{Hz}$ ), 2.21 (1H, m), 4.20 (2H, d,  $J=7.4\text{Hz}$ ), 4.44 (2H, d,  $J=5.6\text{Hz}$ ), 7.09 (1H, d,  $J=1.8\text{Hz}$ ), 7.18-7.34 (4H, m), 7.52 (1H, dd,  $J=8.6$ , 1.8Hz), 8.26 (1H, d,  $J=8.6\text{Hz}$ ).

(5) 6-Bromo-3-chloromethyl-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone (4.5 g, 90%) was obtained as crystals from 6-bromo-4-(4-fluorophenyl)-3-hydroxymethyl-2-isobutyl-1(2H)-isoquinolinone (4.8 g, 11.9 mmol) in the same manner as in Example 106 (5).

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 1.01 (6H, d,  $J=7.0\text{Hz}$ ), 2.21 (1H, m), 4.17 (2H, d,  $J=7.2\text{Hz}$ ), 4.36 (2H, s), 7.11 (1H, d,

J=1.8Hz), 7.19-7.36 (4H, m), 7.60 (1H, dd, J=8.4, 1.8Hz), 8.34 (1H, d, J=8.4Hz).

(6) 3-(Tert-butoxycarbonylaminomethyl)-6-bromo-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone (4.5 g, 86%) was obtained as crystals from 6-bromo-3-chloromethyl-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone (4.5 g, 10.6 mmol) in the same manner as in Example 106 (6), (7).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 0.99 (6H, d, J=7.0 Hz), 1.43 (9H, s), 2.19 (1H, m), 4.05 (2H, d, J=7.2Hz), 4.18 (2H, d, J=5.0Hz), 4.43 (1H, bs), 7.05 (1H, d, J=1.8Hz), 7.21-7.24 (4H, m), 7.56 (1H, dd, J=8.6, 1.8Hz), 8.31 (1H, d, J=8.6Hz).

(7) Methyl 3-(tert-butoxycarbonylaminomethyl)-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carboxylate (1.4 g, 33%) was obtained as crystals from 3-(tert-butoxycarbonylaminomethyl)-6-bromo-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone (4.5 g, 8.9 mmol) in the same manner as in Example 107 (2).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.00 (6H, d, J=7.0Hz), 1.43 (9H, s), 2.24 (1H, m), 3.87 (3H, s), 4.08 (2H, d, J=7.4Hz), 4.21 (2H, d, J=5.0Hz), 4.45 (1H, bs), 7.22-7.26 (4H, m), 7.62 (1H, d, J=2.0Hz), 8.05 (1H, dd, J=8.4, 2.0Hz), 8.52 (1H, d, J=8.4Hz).

(8) 3-(tert-Butoxycarbonylaminomethyl)-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carboxylic acid (1.1 g, 92%) was obtained as a solid from methyl 3-(tert-butoxycarbonylaminomethyl)-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carboxylate (1.2 g, 2.5 mmol) in the same manner as in Example 108 (1).

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.91 (6H, d, J=6.6 Hz), 1.38 (9H, s), 2.17 (2H, m), 3.93 (2H, d, J=7.6Hz), 3.99 (2H, d, J=4.4Hz), 7.33 (1H, bs), 7.37-7.48 (4H, m), 7.51 (1H, d, J=1.4H), 8.00 (1H, dd, J=8.4, 1.4Hz), 8.40 (1H, d, J=8.4Hz).

(9) 3-(Tert-butoxycarbonylaminomethyl)-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carboxamide (0.57 g, 95%) was obtained as a solid from 3-(tert-butoxycarbonylaminomethyl)-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carboxylic acid (0.6 g, 1.3 mmol) in the same manner as in Example 109 (1).

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 1.00 (6H, d,  $J=7.0\text{Hz}$ ), 1.44 (9H, s), 2.26 (2H, m), 4.07 (2H, d,  $J=6.8\text{Hz}$ ), 4.20 (2H, d,  $J=4.8\text{Hz}$ ), 4.62 (1H, bs), 5.12 (1H, bs), 6.03 (1H, bs), 7.22-7.26 (4H, m), 7.38 (1H, s), 7.74 (1H, d,  $J=8.0\text{Hz}$ ), 8.44 (1H, bs).

(10) To a solution of 3-(tert-butoxycarbonylaminomethyl)-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carboxamide (0.5 g, 1.1 mmol) in tetrahydrofuran (2 mL) was added a solution of 4N hydrogen chloride in ethyl acetate (10 mL). The obtained solution was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the residue was crystallized from diethyl ether to give 3-aminomethyl-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carboxamide hydrochloride (0.37 g, 85%) as crystals.

Melting point 218-220°C.

$^1\text{H-NMR}(\text{DMSO}-d_6)$   $\delta$ : 0.92 (6H, d,  $J=6.6\text{Hz}$ ), 2.10 (1H, m), 3.86 (2H, d,  $J=4.6\text{Hz}$ ), 4.08 (2H, d,  $J=7.4\text{Hz}$ ), 7.36-7.46 (5H, m), 7.59 (1H, s), 8.00 (1H, dd,  $J=8.4, 1.6\text{Hz}$ ), 8.17 (1H, s), 8.37 (1H, d,  $J=8.4\text{Hz}$ ), 8.55 (3H, bs).

#### Example 143

Methyl 3-aminomethyl-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carboxylate hydrochloride  
This compound was synthesized from methyl 3-(tert-butoxycarbonylaminomethyl)-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carboxylate in the same manner as in Example 142(10).

$^1\text{H-NMR}(\text{DMSO}-d_6)$   $\delta$ : 0.93 (6H, d,  $J=6.6\text{ Hz}$ ), 2.11 (1H, m), 3.81 (3H, s), 3.88 (2H, s), 4.08 (2H, d,  $J=7.8\text{Hz}$ ), 7.39-

7.52 (5H, m), 8.08 (1H, dd, J=8.4, 1.6Hz), 8.46 (1H, d, J=8.4 Hz), 8.50 (3H, s).

**Example 144**

3-Aminomethyl-4-(4-fluorophenyl)-2-isobutyl-1(2H)-

5 isoquinolinone-6-carboxylic acid hydrochloride

This compound was synthesized from 3-(tert-butoxycarbonylaminoethyl)-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carboxylic acid in the same manner as in Example 142(10).

10 <sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.93 (6H, d, J=6.6 Hz), 2.14 (1H, m), 3.89 (2H, s), 4.08 (1H, s, J=7.8Hz), 7.39-7.52 (5H, m), 8.06 (1H, dd, J=8.4, 1.6Hz), 8.44 (1H, d, J=8.4Hz), 8.50 (3H, bs).

**Example 145**

15 3-Aminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxamide [3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxamide]

To a solution of 3-aminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxamide hydrochloride (2.04 g, 20 5 mmol) in water (20 mL) was added 1N sodium hydroxide (10 mL) and the obtained mixture was stirred at room temperature for 10 min. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous 25 magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate to give 3-aminomethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxamide (0.87 g, 82.9%) as crystals.

30 Melting point 208°C.

Elemental analysis for C<sub>21</sub>H<sub>23</sub>N<sub>3</sub>O<sub>2</sub>

Calculated: C, 72.18; H, 6.63; N, 12.03.

Found: C, 72.10; H, 6.56; N, 11.88.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.01 (6H, d, J=6.6 Hz), 1.42 (2H, bs), 35 2.20-2.34 (1H, m), 3.68 (2H, s), 4.23 (2H, d, J=7.6 Hz), 5.72 (1H, bs), 6.01 (1H, bs), 5.89 (1H, bs), 7.26-7.31



(2H, m), 7.20 (1H, d, J=2.2 Hz), 7.46-7.57 (3H, m), 7.79 (1H, dd, J=1.8, 8.4 Hz), 8.54 (1H, d, J=8.4 Hz).

Powder X-ray crystal diffraction data

Diffraction angle:  $2\theta(^{\circ})$       spacing: d value

5 (angstrom)

5.98	14.8
7.88	11.2
8.44	10.5
17.1	5.19

10 Recrystallization from ethyl acetate in the same manner gave crystals in a different crystal form.

Powder X-ray crystal diffraction data

Diffraction angle:  $2\theta(^{\circ})$       spacing: d value

(angstrom)

15	7.22	11.4
	9.80	9.02
	12.1	7.32
	13.5	6.53
	17.9	4.94
20	19.6	4.52
	20.6	4.30
	21.8	4.08

#### Example 146

3-(Aminomethyl)-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide hydrochloride

25 (1) A solution of 4-bromophthalic anhydride (22.70 g, 100 mmol) and ethyl 2-(cyclopropylmethylamino)acetate (18.87 g, 120 mmol) in tetrahydrofuran (150 mL) was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylformamide (150 mL), and potassium carbonate 30 (14.82 g, 100 mmol) and ethyl iodide (9.6 mL, 120 mmol) were added thereto. The mixture was stirred at room

temperature for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in ethanol (150 mL) and 20% sodium ethoxide ethanol solution (68.10 g, 200 mmol) was added thereto. The mixture was stirred at room temperature for 1 h. The reaction mixture was poured into 1N hydrochloric acid (300 mL) and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography and the component eluted earlier was concentrated to give ethyl 7-bromo-2-cyclopropylmethyl-4-hydroxy-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (11.14 g, 30.4%) as crystals. Melting point 105-105.5°C.

Elemental analysis for  $C_{16}H_{16}NO_4Br$

Calculated: C, 52.48; H, 4.40; N, 3.82.

Found: C, 52.50; H, 4.31; N, 3.80.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.32-0.54 (4H, m), 0.97-1.14 (1H, m), 1.47 (3H, t,  $J=7.2$  Hz), 4.34 (2H, d,  $J=7.0$  Hz), 4.45 (2H, d,  $J=7.2$  Hz), 7.85 (1H, dd,  $J=2.0, 8.6$  Hz), 8.02 (1H, d,  $J=8.6$  Hz), 8.59 (1H, d,  $J=2.6$  Hz), 11.25 (1H, s).

The component eluted later was concentrated to give ethyl 6-bromo-2-cyclopropylmethyl-4-hydroxy-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (11.02 g, 30.1%) as crystals.

Melting point 64-65°C.

Elemental analysis for  $C_{16}H_{16}NO_4Br$

Calculated: C, 52.48; H, 4.40; N, 3.82.

Found: C, 52.36; H, 4.31; N, 3.87.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.32-0.54 (4H, m), 0.97-1.13 (1H, m), 1.48 (3H, t,  $J=7.2$  Hz), 4.33 (2H, d,  $J=6.6$  Hz), 4.52 (2H, d,  $J=7.2$  Hz), 7.78 (1H, dd,  $J=2.0, 8.5$  Hz), 8.29 (1H, d,  $J=8.5$  Hz), 8.30 (1H, d,  $J=2.0$  Hz), 11.16 (1H, s).

(2) To a solution of ethyl 6-bromo-2-cyclopropylmethyl-4-hydroxy-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (7.32 g, 20 mmol), 1-butanol (2.7 mL, 30 mmol) and tributylphosphine (10.0 mL, 40 mmol) in tetrahydrofuran (100 mL) was added 1,1'-(azodicarbonyl)dipiperidine (10.09 g, 40 mmol) and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to give ethyl 6-bromo-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (7.24 g, 85.8%) as an oil.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.39-0.57 (4H, m), 1.02 (3H, t, J=7.1 Hz), 1.13-1.31 (1H, m), 1.45 (3H, t, J=7.2 Hz), 1.46-1.63 (2H, m), 1.73-1.87 (2H, m), 3.90 (2H, d, J=7.0 Hz), 3.96 (2H, t, J=6.6 Hz), 4.47 (2H, q, J=7.2 Hz), 7.65 (1H, dd, J=2.0, 8.6 Hz), 7.78 (1H, d, J=2.0 Hz), 8.29 (1H, dd, J=5.4, 8.6 Hz).

(3) To a solution of ethyl 6-bromo-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (7.18 g, 17 mmol) in tetrahydrofuran (20 mL) and ethanol (20 mL) was added an aqueous solution (10 mL) of sodium hydroxide (2.04 g, 51 mmol). The obtained mixture was refluxed under heating for 12 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give 6-bromo-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (6.41 g, 95.7%) as crystals.

Melting point 166-167°C.

Elemental analysis for C<sub>18</sub>H<sub>20</sub>NO<sub>4</sub>Br  
Calculated: C, 54.84; H, 5.11; N, 3.55.

Found: C, 54.78; H, 4.98; N, 3.27.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.41-0.57 (4H, m), 1.00 (3H, t,  $J=7.4$  Hz), 1.22-1.35 (1H, m), 1.45-1.63 (2H, m), 1.75-1.89 (2H, m), 3.98-4.08 (4H, m), 7.63 (1H, dd,  $J=1.8, 8.8$  Hz),  
5 7.68 (1H, bs), 7.82 (1H, d,  $J=1.8$  Hz), 8.24 (1H, d,  $J=8.8$  Hz).

(4) To a solution of 6-bromo-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (6.31 g, 16 mmol) in  
10 tetrahydrofuran (50 mL) were added oxalyl chloride (1.7 mL, 19.2 mmol) and  $N,N$ -dimethylformamide (2 drops), and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in  
15 tetrahydrofuran (20 mL). The obtained solution was added dropwise to a suspension of sodium tetrahydroborate (2.11 g, 56 mmol) in 1,2-dimethoxyethane (30 mL) at  $0^\circ\text{C}$ . The obtained mixture was stirred at  $0^\circ\text{C}$  for 1 h. The reaction mixture was poured  
20 into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to  
25 give 6-bromo-4-butoxy-2-cyclopropylmethyl-3-hydroxymethyl-1(2H)-isoquinolinone (5.87 g, 96.5%) as crystals.

Melting point  $111-112^\circ\text{C}$ .

Elemental analysis for  $\text{C}_{18}\text{H}_{22}\text{NO}_3\text{Br}$

30 Calculated: C, 56.85; H, 5.83; N, 3.68.

Found: C, 56.69; H, 5.67; N, 3.59.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.42-0.58 (4H, m), 1.04 (3H, t,  $J=7.1$  Hz), 1.12-1.25 (1H, m), 1.49-1.68 (2H, m), 1.79-1.93 (2H, m), 2.48 (1H, bs), 3.88 (2H, t,  $J=6.6$  Hz), 4.19 (2H, d,  $J=6.6$  Hz),  
35 4.83 (2H, s), 7.56 (1H, dd,  $J=2.0, 8.6$  Hz), 7.79 (1H, d,  $J=2.0$  Hz), 8.20 (1H, d,  $J=8.8$  Hz).

(5) To a solution of 6-bromo-4-butoxy-2-cyclopropylmethyl-3-hydroxymethyl-1(2H)-isoquinolinone (5.70 g, 15 mmol) in toluene (50 mL) was added thionyl chloride (2.2 mL, 30 mmol). The obtained mixture was  
5 refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution, and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under  
10 reduced pressure to give 6-bromo-4-butoxy-3-chloromethyl-2-cyclopropylmethyl-1(2H)-isoquinolinone (5.72 g, 95.7%) as crystals.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.44-0.61 (4H, m), 1.02-1.30 (4H, m), 1.53-1.68 (2H, m), 1.71-1.97 (2H, m), 4.00 (2H, t, J=6.4  
15 Hz), 4.21 (2H, d, J=6.6 Hz), 4.84 (2H, s), 7.63 (1H, dd, J=1.8, 8.4 Hz), 7.88 (1H, d, J=1.8 Hz), 8.29 (1H, d, J=8.4 Hz).

(6) A solution of 6-bromo-4-butoxy-3-chloromethyl-2-cyclopropylmethyl-1(2H)-isoquinolinone (5.58 g, 14 mmol)  
20 and potassium phthalimide (3.89 g, 21 mmol) in N,N-dimethylformamide (50 mL) was stirred at room temperature for 5 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried  
25 over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran - n-hexane to give 2-[(6-bromo-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-  
30 dione (6.57 g, 94.7%) as crystals.

Melting point 156-157°C.

Elemental analysis for C<sub>26</sub>H<sub>25</sub>N<sub>2</sub>O<sub>4</sub>Br

Calculated: C, 61.30; H, 4.95; N, 5.50.

Found: C, 61.39; H, 5.06; N, 5.47.

35 <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.45-0.50 (4H, m), 0.97-1.08 (4H, m), 1.44-1.61 (1H, m), 1.79-1.93 (2H, m), 3.99 (2H, t, J=6.7

Hz), 4.16 (2H, d, J=6.2 Hz), 5.07 (2H, s), 7.59 (1H, dd, J=2.0, 8.8 Hz), 7.71-7.85 (4H, m), 7.86 (1H, d, J=2.0 Hz), 8.27 (1H, d, J=8.8 Hz).

(7) To a solution of 2-[(6-bromo-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione (6.62 g, 13 mmol) in ethanol (50 mL) was added hydrazine monohydrate (0.13 mL, 2.7 mmol). The obtained mixture was refluxed under heating for 1 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (30 mL) and di-t-butyl dicarbonate (4.5 mL, 19.5 mmol) was added thereto. The obtained mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - n-hexane to give tert-butyl (6-bromo-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (4.41 g, 70.8%) as crystals.

Melting point 118-119°C.

Elemental analysis for  $C_{23}H_{31}N_2O_4Br$

Calculated: C, 57.62; H, 6.52; N, 5.84.

Found: C, 57.79; H, 6.37; N, 5.71.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.50-0.55 (4H, m), 1.05 (3H, t, J=7.3 Hz), 1.13-1.26 (1H, m), 1.46 (9H, s), 1.47-1.68 (2H, m), 1.80-1.94 (2H, m), 3.86 (2H, t, J=6.5 Hz), 4.09 (2H, d, J=7.0 Hz), 4.53 (2H, d, J=5.6 Hz), 4.79 (1H, bs), 7.58 (1H, dd, J=2.0, 8, 6 Hz), 7.82 (1H, d, J=2.0 Hz), 8.26 (1H, d, J=8.6 Hz).

(8) A mixture of tert-butyl (6-bromo-4-butoxy-2-

cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinoliny)-  
methylcarbamate (4.08 g, 8.5 mmol), 1,3-  
bis(diphenylphosphino)propane (0.35 g, 0.85 mmol) and  
triethylamine (1.3 mL, 9.4 mmol) in dimethyl sulfoxide  
5 (60 mL) and methanol (40 mL) was stirred under a carbon  
monoxide atmosphere at room temperature for 30 min. To  
the obtained mixture was added palladium acetate (0.19 g,  
0.85 mmol) and the mixture was stirred under a carbon  
monoxide atmosphere at 70°C for 15 h. The reaction  
10 mixture was poured into water and extracted with ethyl  
acetate. After washing the extract with water, the  
extract was dried over anhydrous magnesium sulfate and  
concentrated under reduced pressure. The residue was  
purified by silica gel column chromatography to give  
15 methyl 4-butoxy-3-[[ (tert-butoxycarbonyl)amino]methyl]-  
2-cyclopropylmethyl-1-oxo-1,2-dihydro-6-  
isoquinolinecarboxylate (3.41 g, 87.7%) as crystals.  
Melting point 139-140°C.

Elemental analysis for  $C_{25}H_{34}N_2O_6$

20 Calculated: C, 65.48; H, 7.47; N, 6.11.

Found: C, 65.59; H, 7.53; N, 6.13.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.52-0.55 (4H, m), 1.06 (3H, t,  $J=7.4$   
Hz), 1.15-1.30 (1H, m), 1.46 (9H, s), 1.53-1.68 (2H, m),  
1.83-1.97 (2H, m), 3.91 (2H, t,  $J=6.4$  Hz), 3.99 (3H, s),  
25 3.91 (2H, d,  $J=6.6$  Hz), 4.56 (2H, d,  $J=5.4$  Hz), 4.81 (1H,  
bs), 8.09 (1H, dd,  $J=1.6, 8.4$  Hz), 8.40 (1H, d,  $J=1.6$   
Hz), 8.48 (1H, d,  $J=8.4$  Hz).

(9) To a solution of methyl 4-butoxy-3-[[ (tert-  
butoxycarbonyl)amino]methyl]-2-cyclopropylmethyl-1-oxo-  
30 1,2-dihydro-6-isoquinolinecarboxylate (2.98 g, 6.5 mmol)  
in tetrahydrofuran (10 mL) and methanol (10 mL) was  
added 1N sodium hydroxide (10 mL). The obtained mixture  
was stirred at room temperature for 2 h. The reaction  
mixture was poured into water, acidified with 1N  
35 hydrochloric acid and extracted with ethyl acetate. The  
extract was washed with brine, dried over anhydrous

magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give 4-butoxy-3-[[ (tert-butoxycarbonyl)amino]methyl]-2-

- 5 cyclopropylmethyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid (2.62 g, 90.7%) as crystals. Melting point 197-198°C.

Elemental analysis for  $C_{24}H_{32}N_2O_6$

Calculated: C, 64.85; H, 7.26; N, 6.30.

- 10 Found: C, 64.95; H, 7.26; N, 6.29.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.51-0.53 (4H, m), 1.07 (3H, t,  $J=7.3$  Hz), 1.13-1.30 (1H, m), 1.50 (9H, s), 1.53-1.72 (2H, m), 1.85-1.99 (2H, m), 3.91 (2H, t,  $J=6.2$  Hz), 4.09 (2H, d,  $J=6.6$  Hz), 4.56 (2H, d,  $J=5.0$  Hz), 4.47 (1H, bs), 8.08 (1H, d,  $J=8.5$  Hz), 8.30 (1H, bs), 8.39 (1H, d,  $J=8.5$  Hz).

- 15 (10) A solution of 4-butoxy-3-[[ (tert-butoxycarbonyl)amino]methyl]-2-cyclopropylmethyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid (0.89 g, 2 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

- 20 hydrochloride (0.77 g, 4 mmol) and 1-hydroxybenzotriazole ammonium salt (0.61 g, 4 mmol) in  $N,N$ -dimethylformamide (10 mL) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The

- 25 extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give 4-butoxy-3-[[ (tert-butoxycarbonyl)amino]methyl]-2-cyclopropylmethyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide (0.82 g, 93.2%) as crystals. Melting point 202-203°C.

Elemental analysis for  $C_{24}H_{33}N_3O_5$

Calculated: C, 64.99; H, 7.50; N, 9.47.

- 35 Found: C, 64.89; H, 7.68; N, 9.42.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.52-0.56 (4H, m), 1.03 (3H, t,  $J=7.1$



Hz), 1.18-1.29 (1H, m), 1.48 (9H, s), 1.49-1.66 (2H, m),  
1.86-1.94 (2H, m), 3.87 (2H, t, J=6.6 Hz), 4.10 (2H, d,  
J=6.6 Hz), 4.54 (2H, d, J=5.4 Hz), 5.24 (1H, bs), 6.03  
(1H, bs), 6.60 (1H, bs), 7.72 (1H, dd, J=1.6, 8.4 Hz),  
5 8.04 (1H, d, J=1.6 Hz), 8.29 (1H, d, J=8.4 Hz).

(11) To a solution of 4-butoxy-3-[[tert-  
butoxycarbonyl)amino]methyl]-2-cyclopropylmethyl-1-oxo-  
1,2-dihydro-6-isoquinolinecarboxamide (0.27 g, 0.6 mmol)  
in ethyl acetate (5 mL) was added a solution of 4N  
10 hydrogen chloride in ethyl acetate (5 mL) and the  
obtained solution was stirred at room temperature for 1  
h. The reaction mixture was concentrated under reduced  
pressure, and the precipitated crystals were  
recrystallized from methanol-diethyl ether to give 3-  
15 (aminomethyl)-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-  
dihydro-6-isoquinolinecarboxamide hydrochloride (0.21 g,  
91.3%) as crystals.

Melting point 164-165°C.

Elemental analysis for  $C_{19}H_{26}N_3O_3Cl \cdot 0.5H_2O$

20 Calculated: C, 58.68; H, 7.00; N, 10.81.

Found: C, 59.03; H, 6.85; N, 10.82.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.45-0.49 (4H, m), 1.01 (3H, t, J=7.3  
Hz), 1.09-1.21 (1H, m), 1.52-1.63 (2H, m), 1.83-1.99 (2H,  
m), 3.99 (2H, t, J=5.9 Hz), 4.08 (2H, d, J=6.4 Hz), 4.23  
25 (2H, s), 7.71 (1H, s), 8.05 (1H, d, J=8.2 Hz), 8.23 (1H,  
s), 8.33 (1H, d, J=8.2 Hz), 8.38 (1H, s), 8.68 (3H, bs).

#### Example 147

3-(Aminomethyl)-4-butoxy-2-cyclopropylmethyl-6-(1,3-  
oxazol-5-yl)-1(2H)-isoquinolinone hydrochloride

30 (1) To a solution of 4-butoxy-3-[[tert-  
butoxycarbonyl)amino]methyl]-2-cyclopropylmethyl-1-oxo-  
1,2-dihydro-6-isoquinolinecarboxylic acid (Example 146  
(9)) (0.45 g, 3.5 mmol) and N-methylmorpholine (0.13 mL,  
1.2 mmol) in tetrahydrofuran (10 mL) was added ethyl  
35 chloroformate (0.12 mL, 1.2 mmol) at 0°C, and the  
mixture was stirred at 0°C for 10 min. To the obtained

mixture were added sodium tetrahydroborate (0.11 g, 3 mmol) and methanol (5 mL), and the mixture was stirred at 0°C for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was  
5 washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The precipitated crystals were recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl (4-butoxy-2-cyclopropylmethyl-6-hydroxymethyl-1-oxo-1,2-  
10 dihydro-3-isoquinolinyl)methylcarbamate (0.33 g, 76.7%) as crystals.

Melting point 171-172°C.

Elemental analysis for  $C_{24}H_{34}N_2O_5$

Calculated: C, 66.95; H, 7.96; N, 6.51.

15 Found: C, 66.65; H, 7.82; N, 6.63.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.51-0.56 (4H, m), 1.00 (3H, t,  $J=7.3$  Hz), 1.19-1.26 (1H, m), 1.49-1.57 (11H, m), 1.79-1.93 (2H, m), 2.27 (1H, bs), 3.82 (2H, t,  $J=6.8$  Hz), 4.07 (2H, d,  $J=6.6$  Hz), 4.51 (2H, d,  $J=5.4$  Hz), 4.80 (2H, s), 5.53  
20 (1H, s), 7.38 (1H, d,  $J=8.2$  Hz), 7.46 (1H, s), 8.13 (1H, d,  $J=8.2$  Hz).

(2) To a solution of 4 tert-butyl (4-butoxy-2-cyclopropylmethyl-6-hydroxymethyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.45 g, 3.5 mmol) in  
25 tetrahydrofuran (10 mL) was added manganese dioxide (0.12 g) and the mixture was stirred at room temperature for 12 h. Manganese dioxide was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography  
30 to give tert-butyl (4-butoxy-2-cyclopropylmethyl-6-formyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.33 g, 76.7%) as crystals.

Melting point 151-152°C.

Elemental analysis for  $C_{24}H_{32}N_2O_5$

35 Calculated: C, 67.27; H, 7.53; N, 6.54.

Found: C, 67.08; H, 7.55; N, 6.54.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.53-0.56 (4H, m), 1.06 (3H, t, J=7.3 Hz), 1.16-1.28 (1H, m), 1.47 (9H, s), 1.55-1.68 (2H, m), 1.87-1.96 (2H, m), 3.92 (2H, t, J=6.4 Hz), 4.14 (2H, d, J=6.6 Hz), 4.57 (2H, d, J=5.7 Hz), 4.82 (1H, bs), 7.96  
5 (1H, dd, J=1.8, 8.4 Hz), 8.19 (1H, d, J=1.8 Hz), 8.57 (1H, d, J=8.4 Hz), 10.19 (1H, s).

(3) A solution of tert-butyl (4-butoxy-2-cyclopropylmethyl-6-formyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.34 g, 0.8 mmol), p-  
10 toluenesulfonylmethyl isocyanide (0.16 g, 0.8 mmol) and potassium carbonate (0.22 g, 1.6 mmol) in methanol (10 mL) was refluxed under heating for 30 min. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over  
15 anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography and the precipitated crystals were recrystallized from ethyl acetate - diisopropyl  
20 ether to give tert-butyl [4-butoxy-2-cyclopropylmethyl-6-(1,3-oxazol-5-yl)-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.33 g, 76.7%) as crystals.

Melting point 160-161°C.

Elemental analysis for C<sub>26</sub>H<sub>33</sub>N<sub>3</sub>O<sub>5</sub>

25 Calculated: C, 66.79; H, 7.11; N, 8.99.

Found: C, 66.63; H, 7.14; N, 9.01.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.52-0.56 (4H, m), 1.07 (3H, t, J=7.2 Hz), 1.12-1.26 (1H, m), 1.47 (9H, s), 1.58-1.71 (2H, m), 1.87-1.96 (2H, m), 3.92 (2H, t, J=6.6 Hz), 4.12 (2H, d, J=6.6 Hz), 4.56 (2H, d, J=5.7 Hz), 4.84 (1H, bs), 7.53  
30 (1H, s), 7.75 (1H, dd, J=1.5, 8.4 Hz), 7.97 (1H, d, J=1.5 Hz), 8.02 (1H, s), 8.46 (1H, d, J=8.4 Hz).

(4) To a solution of tert-butyl [4-butoxy-2-cyclopropylmethyl-6-(1,3-oxazol-5-yl)-1-oxo-1,2-dihydro-  
35 3-isoquinolinyl]methylcarbamate (0.19 g, 0.4 mmol) in ethyl acetate (5 mL) was added a solution of 4N hydrogen

chloride in ethyl acetate (5 mL) and the obtained solution was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from  
5 methanol-diethyl ether to give 3-(aminomethyl)-4-butoxy-2-cyclopropylmethyl-6-(1,3-oxazol-5-yl)-1(2H)-isoquinolinone hydrochloride (0.15 g, 93.8%) as crystals. Melting point 124-126°C.

Elemental analysis for  $C_{21}H_{26}N_3O_3Cl \cdot 1.25H_2O$

10 Calculated: C, 59.15; H, 6.74; N, 9.85.

Found: C, 59.12; H, 6.58; N, 9.71.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.46-0.49 (4H, s), 1.03 (3H, t,  $J=7.2$  Hz), 1.15-1.28 (1H, m), 1.54-1.69 (2H, m), 1.83-1.95 (2H, m), 3.99 (2H, t,  $J=6.2$  Hz), 4.08 (2H, d,  $J=6.6$  Hz), 4.23  
15 (2H, d,  $J=5.4$  Hz), 7.99-8.01 (3H, m), 8.36 (1H, d,  $J=9.2$  Hz), 8.63 (1H, s), 8.74 (3H, bs).

#### Example 148

(E)-3-[3-(Aminomethyl)-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide  
20 hydrochloride

(1) To a solution of ethyl diethylphosphonoacetate (0.99 mL, 5 mmol) in N,N-dimethylformamide (30 mL) was added sodium hydride (0.20 g, 5 mmol) (60% in oil) and the mixture was stirred at room temperature for 10 min. To  
25 the obtained mixture was added a solution of tert-butyl (4-butoxy-2-cyclopropylmethyl-6-formyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (Example 2 (2)) (2.14 g, 5 mmol) in N,N-dimethylformamide (20 mL) and the mixture was stirred at room temperature for 3 h.

30 The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give  
35 ethyl (E)-3-(4-butoxy-3-[[[tert-butoxycarbonyl]amino]methyl]-2-cyclopropylmethyl-1-oxo-

1,2-dihydro-3-isoquinolinyl)-2-propenate (1.92 g, 77.1%) as crystals.

Melting point 166-167°C.

Elemental analysis for  $C_{28}H_{38}N_2O_6$

5 Calculated: C, 67.45; H, 7.68; N, 5.62.

Found: C, 67.40; H, 7.65; N, 5.44.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.51-0.55 (4H, m), 1.06 (3H, t,  $J=7.1$  Hz), 1.14-1.27 (1H, m), 1.37 (3H, t,  $J=7.2$  Hz), 1.46 (9H, s), 1.47-1.69 (2H, m), 1.83-1.97 (2H, m), 3.89 (2H, t,  $J=6.4$  Hz), 4.12 (2H, d,  $J=6.6$  Hz), 4.30 (2H, q,  $J=7.2$  Hz), 4.55 (2H, d,  $J=5.4$  Hz), 4.78 (1H, bs), 6.58 (1H, d,  $J=15.8$  Hz), 7.66 (1H, dd,  $J=1.8, 8.4$  Hz), 7.78 (1H, d,  $J=1.8$  Hz), 7.79 (1H, d,  $J=15.8$  Hz), 8.42 (1H, d,  $J=8.4$  Hz).

15 (2) To a solution of ethyl (E)-3-(4-butoxy-3-[[tert-butoxycarbonyl]amino]methyl]-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinyl)-2-propenate (1.00 g, 2 mmol) in tetrahydrofuran (10 mL) and ethanol (10 mL) was added 1N sodium hydroxide (4 mL). The obtained mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran - diisopropyl ether to give (E)-3-(4-butoxy-3-[[tert-butoxycarbonyl]amino]methyl]-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinyl)-2-propenic acid (0.92 g, 97.9%) as crystals.

30 Melting point 229-230°C.

Elemental analysis for  $C_{26}H_{34}N_2O_6$

Calculated: C, 66.36; H, 7.28; N, 5.95.

Found: C, 66.05; H, 7.22; N, 5.66.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.50-0.55 (4H, m), 1.07 (3H, t,  $J=7.3$  Hz), 1.12-1.28 (1H, m), 1.48 (9H, s), 1.49-1.70 (2H, m), 1.84-1.98 (2H, m), 3.89 (2H, t,  $J=6.6$  Hz), 4.10 (2H, d,

J=6.6 Hz), 4.55 (2H, d, J=5.0 Hz), 5.12 (1H, bs), 6.59 (1H, d, J=16.0 Hz), 7.64 (1H, d, J=8.2 Hz), 7.73 (1H, s), 7.85 (1H, d, J=16.0 Hz), 8.38 (1H, d, J=8.2 Hz).

- (3) A solution of (E)-3-(4-butoxy-3-[[tert-butoxycarbonyl)amino]methyl]-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinyl)-2-propenic acid (0.71 g, 1.5 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.58 g, 3 mmol) and 1-hydroxybenzotriazole ammonium salt (0.46 g, 3 mmol) in N,N-dimethylformamide (10 mL) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran - diisopropyl ether to give (E)-3-(4-butoxy-3-[[tert-butoxycarbonyl)amino]methyl]-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinyl)-2-propenamide (0.67 g, 95.7%) as crystals.

- Melting point 198-199°C.

Elemental analysis for  $C_{26}H_{35}N_3O_5 \cdot 0.5H_2O$

Calculated: C, 65.87; H, 7.55; N, 8.86.

Found: C, 65.86; H, 7.89; N, 8.68.

- $^1H$ -NMR(CDCl<sub>3</sub>)  $\delta$ : 0.50-0.54 (4H, m), 1.04 (3H, t, J=7.4 Hz), 1.12-1.26 (1H, m), 1.47 (9H, s), 1.48-1.67 (2H, m), 1.81-1.95 (2H, m), 3.88 (2H, t, J=6.4 Hz), 4.10 (2H, d, J=6.6 Hz), 4.54 (2H, d, J=5.2 Hz), 5.40 (1H, bs), 5.89 (1H, bs), 6.05 (1H, bs), 6.60 (1H, d, J=15.8 Hz), 7.56 (1H, dd, J=1.5, 8.4 Hz), 7.69 (1H, d, J=1.5 Hz), 7.73 (1H, d, J=15.8 Hz), 8.31 (1H, d, J=8.4 Hz).

- (4) To a solution of (E)-3-(4-butoxy-3-[[tert-butoxycarbonyl)amino]methyl]-1-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinyl)-2-propenamide (0.38 g, 0.8 mmol) in ethyl acetate (5 mL) was added a solution of 4N hydrogen chloride in ethyl acetate (5 mL) and the obtained solution was stirred at room temperature for 2

h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol - diisopropyl ether to give (E)-3-[3-(aminomethyl)-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide hydrochloride (0.31 g, 96.9%) as crystals. Melting point 188-190°C.

Elemental analysis for  $C_{21}H_{28}N_3O_3Cl \cdot 2H_2O$

Calculated: C, 57.07; H, 7.30; N, 9.51.

10 Found: C, 56.82; H, 7.06; N, 9.49.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.45-0.48 (4H, m), 1.02 (3H, t,  $J=6.9$  Hz), 1.13-1.24 (1H, m), 1.47-1.69 (2H, m), 1.79-1.99 (2H, m), 4.05 (2H, bs), 4.22 (2H, bs), 4.32 (2H, bs), 6.85 (1H, d,  $J=15.4$  Hz), 7.28 (1H, bs), 7.63 (1H, d,  $J=15.4$  Hz), 7.80-7.88 (3H, m), 8.30 (1H, d,  $J=7.0$  Hz), 8.68 (3H, bs).

#### Example 149

2-[[3-(Aminomethyl)-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-6-isoquinolinyl]oxy]acetamide hydrochloride

20 (1) A solution of 4-fluorophthalic anhydride (24.99 g, 150 mmol) and ethyl 2-(cyclopropylmethylamino)acetate (23.58 g, 150 mmol) in tetrahydrofuran (200 mL) was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylformamide (200 mL) and potassium carbonate (20.73 g, 150 mmol) and ethyl iodide (14.4 mL, 180 mmol) were added. The mixture was stirred at room temperature for 3 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in ethanol (300 mL) and a solution of 20% sodium ethoxide ethanol solution (102 g, 300 mmol) was

added thereto. The mixture was stirred at room temperature for 1 h. The reaction mixture was poured into 1N hydrochloric acid (300 mL) and extracted with ethyl acetate. The extract was washed with brine, dried  
5 over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography and the component eluted earlier was concentrated to give ethyl 2-cyclopropylmethyl-7-fluoro-4-hydroxy-1-oxo-1,2-dihydro-  
10 3-isoquinolinecarboxylate (13.11 g, 28.6%) as crystals. Melting point 88-89°C.

Elemental analysis for  $C_{16}H_{16}NO_4F$

Calculated: C, 62.94; H, 5.28; N, 4.59.

Found: C, 62.96; H, 5.23; N, 4.61.

15  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.34-0.52 (4H, m), 1.04-1.13 (1H, m), 1.48 (3H, t,  $J=7.2$  Hz), 4.35 (2H, d,  $J=6.9$  Hz), 4.51 (2H, d,  $J=7.2$  Hz), 7.44-7.50 (1H, m), 8.09 (1H, dd,  $J=2.6$ , 6.2 Hz), 8.19 (1H, dd,  $J=6.2$ , 8.4 Hz), 11.36 (1H, s).

The component eluted later was concentrated to give  
20 ethyl 2-cyclopropylmethyl-6-fluoro-4-hydroxy-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (9.34 g, 20.4%) as crystals.

Melting point 61-62°C.

Elemental analysis for  $C_{16}H_{16}NO_4F$

25 Calculated: C, 62.94; H, 5.28; N, 4.59.

Found: C, 62.75; H, 5.14; N, 4.64.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.32-0.54 (4H, m), 1.00-1.16 (1H, m), 1.48 (3H, t,  $J=7.2$  Hz), 4.33 (2H, d,  $J=7.0$  Hz), 4.52 (2H, d,  $J=7.2$  Hz), 7.33-7.43 (1H, m), 7.78 (1H, dd,  $J=2.6$ , 9.2 Hz), 8.46 (1H, dd,  $J=5.4$ , 8.8 Hz), 11.14 (1H, s).

30 (2) To a solution of ethyl 2-cyclopropylmethyl-6-fluoro-4-hydroxy-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (9.16 g, 30 mmol), 1-butanol (3.3 mL, 45 mmol) and tributylphosphine (14.9 mL, 60 mmol) in tetrahydrofuran (100 mL) was added 1,1'-(azodicarbonyl)dipiperidine (15.14 g, 60 mmol) and the mixture was stirred at room



temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to give ethyl 4-butoxy-2-cyclopropylmethyl-6-fluoro-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (9.24 g, 85.2%) as an oil.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.39-0.57 (4H, m), 1.01 (3H, t, J=7.3 Hz), 1.12-1.21 (1H, m), 1.41-1.62 (5H, m), 1.73-1.87 (2H, m), 3.91 (2H, d, J=6.8 Hz), 3.96 (2H, t, J=6.6 Hz), 4.47 (2H, q, J=7.3 Hz), 7.19-7.30 (1H, m), 8.73 (1H, dd, J=2.4, 9.4 Hz), 8.46 (1H, dd, J=5.4, 8.8 Hz).

(3) To a solution of ethyl 4-butoxy-2-cyclopropylmethyl-6-fluoro-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (9.03 g, 25 mmol) in tetrahydrofuran (30 mL) and ethanol (30 mL) was added sodium hydroxide (3.00 g, 75 mmol). The obtained mixture was refluxed under heating for 12 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in benzyl alcohol (20 mL) and the obtained solution was added dropwise to a solution of sodium hydride (5.0 g, 125 mmol) (60% in oil) in benzyl alcohol (20 mL). The obtained mixture was stirred at 150°C for 12 h. The reaction mixture was poured into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran - diisopropyl ether to give 6-benzyloxy-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (7.31 g, 69.4%) as crystals. Melting point 178-179°C.

Elemental analysis for C<sub>25</sub>H<sub>27</sub>NO<sub>5</sub>.

Calculated: C, 71.24; H, 6.46; N, 3.32.

Found: C, 71.21; H, 6.68; N, 3.23.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.41-0.52 (4H, m), 0.97 (3H, t, J=7.4 Hz), 1.18-1.32 (1H, m), 1.38-1.57 (2H, m), 1.67-1.80 (2H, m), 3.88 (2H, t, J=6.4 Hz), 4.00 (2H, d, J=7.0 Hz), 5.17 (2H, s), 6.55 (1H, bs), 6.98 (1H, d, J=2.5 Hz), 7.16 (1H, dd, J=2.5, 8.8 Hz), 7.30-7.44 (5H, m), 8.25 (1H, d, J=8.8 Hz).

(4) To a solution of 6-benzyloxy-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (7.16 g, 17 mmol) in tetrahydrofuran (50 mL) were added oxalyl chloride (1.8 mL, 20.4 mmol) and N,N-dimethylformamide (3 drops), and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (30 mL). The obtained solution was added dropwise to a suspension of sodium tetrahydroborate (2.25 g, 59.5 mmol) in 1,2-dimethoxyethane (50 mL) at 0°C. The obtained mixture was stirred at 0°C for 1 h. The reaction mixture was poured into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - n-hexane to give 6-benzyloxy-4-butoxy-2-cyclopropylmethyl-3-hydroxymethyl-1(2H)-isoquinolinone (1.72 g, 57.1%) as crystals. Melting point 96-97°C.

Elemental analysis for C<sub>25</sub>H<sub>29</sub>NO<sub>4</sub>.

Calculated: C, 73.68; H, 7.17; N, 3.44.

Found: C, 73.53; H, 7.10; N, 3.39.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.45-0.55 (4H, m), 1.02 (3H, t, J=7.3 Hz), 1.12-1.24 (1H, m), 1.44-1.62 (2H, m), 1.72-1.86 (2H, m), 3.79 (2H, t, J=6.6 Hz), 4.17 (2H, d, J=6.4 Hz), 4.82 (2H, d, J=5.2 Hz), 5.19 (2H, s), 7.05 (1H, d, J=2.6 Hz), 7.11 (1H, dd, J=2.6, 8.8 Hz), 7.31-7.48 (5H, m), 8.28

(1H, d, J=8.8 Hz).

(5) To a suspension of 6-benzyloxy-4-butoxy-2-cyclopropylmethyl-3-hydroxymethyl-1(2H)-isoquinolinone (6.11 g, 15 mmol) in toluene (50 mL) was added thionyl chloride (2.2 mL, 30 mmol). The obtained mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 6-benzyloxy-4-butoxy-3-chloromethyl-2-cyclopropylmethyl-1(2H)-isoquinolinone (6.17 g, 96.7%) as crystals.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.47-0.55 (4H, m), 1.03 (3H, t, J=7.5 Hz), 1.06-1.18 (1H, m), 1.48-1.63 (2H, m), 1.79-1.86 (2H, m), 3.90 (2H, t, J=6.6 Hz), 4.20 (2H, d, J=6.6 Hz), 4.84 (2H, s), 5.22 (2H, s), 7.14-7.26 (2H, m), 7.34-7.47 (5H, m), 8.36 (1H, d, J=9.0 Hz).

(6) A solution of 6-benzyloxy-4-butoxy-3-chloromethyl-2-cyclopropylmethyl-1(2H)-isoquinolinone (5.96 g, 14 mmol) and potassium phthalimide (3.89 g, 21 mmol) in N,N-dimethylformamide (50 mL) was stirred at room temperature for 6 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give 2-[(6-benzyloxy-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione (7.14 g, 95.1%) as crystals.

Melting point 127-128°C.

Elemental analysis for C<sub>33</sub>H<sub>32</sub>N<sub>2</sub>O<sub>5</sub>

Calculated: C, 73.86; H, 6.01; N, 5.22.

Found: C, 73.73; H, 5.79; N, 5.22.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.43-0.48 (4H, m), 0.97 (3H, t, J=7.3

Hz), 1.01-1.04 (1H, m), 1.37-1.55 (2H, m), 1.71-1.86 (2H, m), 3.89 (2H, t, J=6.8 Hz), 4.15 (2H, d, J=6.2 Hz), 5.06 (2H, s), 5.20 (2H, s), 7.12-7.17 (2H, m), 7.30-7.46 (5H, m), 7.70-7.86 (4H, m), 8.32-8.38 (1H, m).

- 5 (7) To a solution of 2-[(6-benzyloxy-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione (6.97 g, 13 mmol) in ethanol (50 mL) was added hydrazine monohydrate (1.9 mL, 39 mmol). The obtained mixture was  
10 refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under  
15 reduced pressure. The residue was dissolved in tetrahydrofuran (50 mL) and di-t-butyl dicarbonate (4.5 mL, 19.5 mmol) was added thereto. The obtained mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl  
20 acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - n-hexane to give tert-butyl (6-benzyloxy-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (6.34 g,  
25 96.4%) as crystals.

Melting point 106-107°C.

Elemental analysis for  $C_{30}H_{38}N_2O_5 \cdot 0.25H_2O$

Calculated: C, 70.50; H, 7.59; N, 5.48.

- 30 Found: C, 70.61; H, 7.48; N, 5.45.

- $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.49-0.52 (4H, m), 1.02 (3H, t, J=7.3 Hz), 1.15-1.26 (1H, m), 1.46 (9H, s), 1.51-1.62 (2H, m), 1.72-1.87 (2H, m), 3.77 (2H, t, J=6.5 Hz), 4.08 (2H, d, J=5.6 Hz), 4.51 (2H, d, J=5.6 Hz), 4.79 (1H, bs), 5.21  
35 (2H, s), 7.07 (1H, d, J=2.6 Hz), 7.14 (1H, dd, J=2.6, 8.8 Hz), 7.33-7.49 (5H, m), 8.34 (1H, d, J=8.8 Hz).

(8) A suspension of tert-butyl (6-benzyloxy-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinyl)-methylcarbamate (6.08 g, 12 mmol) and 5% palladium carbon (2.0 g) in tetrahydrofuran (30 mL) and ethanol  
5 (30 mL) was stirred under a hydrogen atmosphere at room temperature for 2 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran - diisopropyl ether to give tert-butyl  
10 (4-butoxy-2-cyclopropylmethyl-6-hydroxy-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (4.87 g, 97.6%) as crystals.

Melting point 164-166°C.

Elemental analysis for  $C_{23}H_{32}N_2O_5$

15 Calculated: C, 66.32; H, 7.74; N, 6.73.

Found: C, 66.16; H, 7.69; N, 6.82.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.48-0.52 (4H, m), 0.96 (3H, t,  $J=7.4$  Hz), 1.13-1.26 (1H, m), 1.45-1.58 (11H, m), 1.69-1.84 (2H, m), 3.83 (2H, t,  $J=6.2$  Hz), 4.12 (2H, d,  $J=6.6$  Hz),  
20 4.53 (2H, d,  $J=5.2$  Hz), 4.89 (1H, bs), 7.06-7.12 (2H, m), 8.25 (1H, d,  $J=8.4$  Hz), 9.24 (1H, bs).

(9) A solution of tert-butyl (4-butoxy-2-cyclopropylmethyl-6-hydroxy-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.42 g, 1 mmol), 2-  
25 iodoacetamide (0.27 g, 1.5 mmol) and 1,8-diazabicyclo[5.4.0]-7-undecene (0.22 mL, 1.5 mmol) in N,N-dimethylformamide (10 mL) was stirred at 80°C for 10 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed  
30 with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [6-(2-amino-2-oxoethoxy)-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinyl]-  
35 methylcarbamate (0.36 g, 76.6%) as crystals.  
Melting point 209-210°C.

Elemental analysis for  $C_{25}H_{35}N_3O_6$

Calculated: C, 63.41; H, 7.45; N, 8.87.

Found: C, 63.05; H, 7.31; N, 8.61.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.48-0.56 (4H, m), 1.04 (3H, t,  $J=7.2$  Hz), 1.15-1.26 (1H, m), 1.46 (9H, s), 1.48-1.69 (2H, m), 1.80-1.91 (2H, m), 3.86 (2H, t,  $J=6.4$  Hz), 4.09 (2H, d,  $J=6.6$  Hz), 4.53 (2H, d,  $J=5.6$  Hz), 4.62 (2H, s), 4.86 (1H, bs), 5.89 (1H, bs), 6.62 (1H, bs), 7.06-7.12 (2H, m), 8.36 (1H, d,  $J=9.2$  Hz).

(10) To a solution of tert-butyl [6-(2-amino-2-oxoethoxy)-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.28 g, 0.6 mmol) in ethyl acetate (5 mL) was added a solution of 4N hydrogen chloride in ethyl acetate (5 mL) and the obtained solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol - diisopropyl ether to give 2-[[3-(aminomethyl)-4-butoxy-2-cyclopropylmethyl-1-oxo-1,2-dihydro-6-isoquinolinyl]oxy]acetamide hydrochloride (0.23 g, 92.0%) as crystals.

Melting point 133-134°C.

Elemental analysis for  $C_{20}H_{28}N_3O_4Cl \cdot 1.5H_2O$

Calculated: C, 54.98; H, 7.15; N, 9.62.

Found: C, 54.84; H, 6.90; N, 9.54.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.43-0.46 (4H, m), 1.00 (3H, t,  $J=7.1$  Hz), 1.12-1.21 (1H, m), 1.50-1.63 (2H, m), 1.81-1.92 (2H, m), 3.93 (2H, t,  $J=6.1$  Hz), 4.04 (2H, d,  $J=6.2$  Hz), 4.18 (2H, s), 4.64 (2H, s), 7.23 (1H, d,  $J=8.8$  Hz), 7.47 (1H, s), 7.75 (1H, s), 8.21 (1H, d,  $J=8.8$  Hz), 8.68 (3H, s).

#### Example 150

2-[[3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]oxy]acetamide hydrochloride

(1) A solution of 4-fluorophthalic anhydride (24.99 g, 150 mmol) and ethyl 2-(isobutylamino)acetate (23.88 g, 150 mmol) in tetrahydrofuran (200 mL) was stirred at

room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylformamide (200 mL), and potassium carbonate (20.73 g, 150 mmol) and ethyl iodide (14.4 mL, 180 mmol) were added thereto. The mixture was stirred at room temperature for 3 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in ethanol (300 mL) and a solution of 20% sodium ethoxide ethanol solution (102 g, 300 mmol) was added thereto. The mixture was stirred at room temperature for 1 h. The reaction mixture was poured into 1N hydrochloric acid (300 mL) and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography and the component eluted earlier was concentrated to give ethyl 7-fluoro-4-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (19.2 g, 41.7%) as crystals.

Melting point 104-105°C.

Elemental analysis for  $C_{16}H_{18}NO_4F$

Calculated: C, 62.53; H, 5.90; N, 4.56.

Found: C, 62.81; H, 5.99; N, 4.67.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.82 (6H, d,  $J=6.6$  Hz), 1.46 (3H, t,  $J=7.2$  Hz), 1.76-1.89 (1H, m), 4.41 (2H, d,  $J=7.2$  Hz), 4.49 (2H, d,  $J=7.2$  Hz), 7.43-7.50 (1H, m), 8.08-8.21 (2H, m), 11.34 (1H, s).

The component eluted later was concentrated to give ethyl 6-fluoro-4-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (13.41 g, 29.1%) as crystals.

Melting point 91-92°C.

Elemental analysis for  $C_{16}H_{18}NO_4F$

Calculated: C, 62.53; H, 5.90; N, 4.56.

Found: C, 62.73; H, 5.83; N, 4.53.

5  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.82 (6H, d,  $J=6.6$  Hz), 1.46 (3H, t,  $J=7.2$  Hz), 1.74-1.86 (1H, m), 4.40 (2H, d,  $J=7.5$  Hz), 4.49 (2H, d,  $J=7.2$  Hz), 7.34-7.42 (1H, m), 7.75-7.80 (1H, m), 8.45-8.51 (1H, m), 11.12 (1H, s).

(2) To a solution of ethyl 6-fluoro-4-hydroxy-2-  
10 isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (9.22 g, 30 mmol), 1-butanol (3.3 mL, 45 mmol) and tributylphosphine (14.9 mL, 60 mmol) in tetrahydrofuran (100 mL) was added 1,1'-(azodicarbonyl)dipiperidine (15.14 g, 60 mmol) and the mixture was stirred at room  
15 temperature for 3 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to give ethyl 4-butoxy-6-fluoro-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (9.25 g, 84.9%) as an oil.

20  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.91 (6H, d,  $J=6.6$  Hz), 1.01 (3H, t,  $J=7.4$  Hz), 1.45 (3H, t,  $J=7.2$  Hz), 1.46-1.66 (2H, m), 1.74-1.84 (2H, m), 2.05-2.18 (1H, m), 3.88 (2H, d,  $J=7.8$  Hz), 3.95 (2H, t,  $J=6.6$  Hz), 4.46 (2H, q,  $J=7.2$  Hz), 7.27-7.29 (1H, m), 7.34-7.38 (1H, m), 8.44-8.48 (1H, m).

25 (3) To a solution of ethyl 4-butoxy-6-fluoro-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (9.09 g, 25 mmol) in tetrahydrofuran (30 mL) and ethanol (30 mL) was added sodium hydroxide (3.00 g, 75 mmol). The obtained mixture was refluxed under heating for 12 h. The  
30 reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in benzyl alcohol  
35 (20 mL) and the obtained solution was added dropwise to a solution of sodium hydride (5.0 g, 125 mmol) (60% in



oil) in benzyl alcohol (20 mL). The obtained mixture was stirred at 150°C for 12 h. The reaction mixture was poured into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried  
5 over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran - diisopropyl ether to give 6-benzyloxy-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (9.32 g, 88.1%) as  
10 crystals.

Melting point 151-152°C.

Elemental analysis for  $C_{25}H_{29}NO_5$

Calculated: C, 70.90; H, 6.90; N, 3.31.

Found: C, 70.89; H, 6.91; N, 3.37.

15  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.85 (6H, d,  $J=7.0$  Hz), 0.98 (3H, t,  $J=7.3$  Hz), 1.39-1.58 (2H, m), 1.67-1.81 (2H, m), 2.06-2.19 (1H, m), 3.89 (2H, t,  $J=6.6$  Hz), 3.95 (2H, d,  $J=7.8$  Hz), 5.16 (2H, s), 6.96 (1H, d,  $J=2.6$  Hz), 7.17 (1H, dd,  $J=2.6, 9.0$  Hz), 7.32-7.45 (5H, m), 8.23 (1H, d,  $J=9.0$   
20 Hz).

(4) To a solution of 6-benzyloxy-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (7.62 g, 18 mmol) in tetrahydrofuran (50 mL) were added oxalyl chloride (1.9 mL, 21.6 mmol) and N,N-dimethylformamide (2 drops), and the mixture was stirred at room  
25 temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in tetrahydrofuran (30 mL). The obtained solution was added dropwise to a suspension of sodium tetrahydroborate (2.38 g, 63 mmol) in 1,2-  
30 dimethoxyethane (50 mL) at 0°C. The obtained mixture was stirred at 0°C for 1 h. The reaction mixture was poured into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over  
35 anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were

recrystallized from ethyl acetate - diisopropyl ether to give 6-benzyloxy-4-butoxy-3-hydroxymethyl-2-isobutyl-1(2H)-isoquinolinone (7.11 g, 96.5%) as crystals. Melting point 90-91°C.

5 Elemental analysis for  $C_{25}H_{31}NO_4 \cdot 0.25H_2O$

Calculated: C, 72.53; H, 7.67; N, 3.38.

Found: C, 72.86; H, 7.71; N, 3.31.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.92 (6H, d,  $J=6.6$  Hz), 1.02 (3H, t,  $J=7.1$  Hz), 1.48-1.60 (2H, m), 1.72-1.85 (2H, m), 2.11-  
10 2.25 (1H, m), 2.44 (1H, bs), 3.79 (2H, t,  $J=6.4$  Hz), 4.05 (2H, d,  $J=7.4$  Hz), 4.79 (2H, d,  $J=5.4$  Hz), 5.19 (2H, s), 7.06-7.13 (2H, m), 7.34-7.45 (4H, m), 8.28 (1H, d,  $J=8.4$  Hz).

(5) To a suspension of 6-benzyloxy-4-butoxy-3-  
15 hydroxymethyl-2-isobutyl-1(2H)-isoquinolinone (6.96 g, 17 mmol) in toluene (50 mL) was added thionyl chloride (2.5 mL, 34 mmol). The obtained mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution  
20 and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 6-benzyloxy-4-butoxy-3-chloromethyl-2-isobutyl-1(2H)-isoquinolinone (6.90 g, 94.8%) as crystals.

25  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.95 (6H, d,  $J=7.0$  Hz), 1.03 (3H, t,  $J=7.3$  Hz), 1.47-1.65 (2H, m), 1.76-1.90 (2H, m), 2.09-2.23 (1H, m), 3.88 (2H, t,  $J=6.4$  Hz), 4.05 (2H, d,  $J=7.2$  Hz), 4.80 (2H, s), 5.21 (2H, s), 7.13-7.47 (7H, m), 8.36 (1H, d,  $J=8.8$  Hz).

30 (6) A solution of 6-benzyloxy-4-butoxy-3-chloromethyl-2-isobutyl-1(2H)-isoquinolinone (6.85 g, 16 mmol) and potassium phthalimide (4.44 g, 24 mmol) in N,N-dimethylformamide (50 mL) was stirred at room temperature for 6 h. The reaction mixture was poured  
35 into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried

over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 2-[(6-benzyloxy-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-

5 isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione (7.08 g, 82.2%) as an amorphous.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.93-1.01 (9H, m), 1.41-1.55 (2H, m), 1.71-1.85 (2H, m), 2.05-2.22 (1H, m), 3.89 (2H, t, J=6.9 Hz), 4.01 (2H, d, J=7.2 Hz), 5.01 (2H, s), 5.20 (2H, s),  
10 7.13-7.17 (2H, m), 7.30-7.46 (5H, m), 7.68-7.87 (2H, m), 8.32-8.36 (1H, m).

(7) To a solution of 2-[(6-benzyloxy-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione (7.00 g, 13 mmol) in ethanol (50  
15 mL) was added hydrazine monohydrate (1.9 mL, 39 mmol): The obtained mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried  
20 over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (50 mL) and di-*t*-butyl dicarbonate (4.5 mL, 19.5 mmol) was added thereto. The obtained mixture was stirred at room temperature for 1 h. The reaction  
25 mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - *n*-hexane to give  
30 *tert*-butyl (6-benzyloxy-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (6.44 g, 97.4%) as crystals.

Melting point 104-105°C.

Elemental analysis for C<sub>30</sub>H<sub>40</sub>N<sub>2</sub>O<sub>5</sub>

35 Calculated: C, 70.84; H, 7.93; N, 5.51.

Found: C, 70.85; H, 7.70; N, 5.48.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.94 (6H, d, J=7.0 Hz), 1.02 (3H, t, J=7.3 Hz), 1.46-1.62 (11H, m), 1.72-1.86 (2H, m), 2.05-2.22 (1H, m), 3.75 (2H, t, J=6.6 Hz), 3.96 (2H, d, J=7.6 Hz), 4.48 (2H, d, J=5.4 Hz), 4.73 (1H, bs), 5.21 (2H, s),  
5 7.08 (1H, d, J=2.6 Hz), 7.15 (1H, dd, J=2.6, 8.8 Hz), 7.30-7.47 (5H, m), 8.34 (1H, d, J=8.8 Hz).

(8) A suspension of tert-butyl (6-benzyloxy-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (6.10 g, 12 mmol) and 5%  
10 palladium carbon (2.0 g) in tetrahydrofuran (30 mL) and ethanol (30 mL) was stirred under a hydrogen atmosphere at room temperature for 2 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The obtained crystals were recrystallized  
15 from ethyl acetate - diisopropyl ether to give tert-butyl (4-butoxy-6-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (4.86 g, 96.8%) as crystals.

Melting point 185-186°C.

20 Elemental analysis for C<sub>23</sub>H<sub>34</sub>N<sub>2</sub>O<sub>5</sub>

Calculated: C, 66.00; H, 8.19; N, 6.69.

Found: C, 66.02; H, 8.14; N, 6.73.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.95 (6H, d, J=6.6 Hz), 0.96 (3H, t, J=7.0 Hz), 1.46-1.58 (11H, m), 1.72-1.85 (2H, m), 2.06-  
25 2.25 (1H, m), 3.82 (2H, t, J=6.6 Hz), 4.00 (2H, d, J=6.8 Hz), 4.51 (2H, d, J=4.8 Hz), 4.84 (1H, bs), 7.09-7.13 (2H, m), 8.27 (1H, d, J=9.6 Hz), 8.98 (1H, bs).

(9) A solution of tert-butyl (4-butoxy-6-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.42 g, 1 mmol), 2-iodoacetamide (0.27 g, 1.5 mmol) and 1,8-diazabicyclo[5.4.0]-7-undecene (0.22 mL, 1.5 mmol) in  
30 N,N-dimethylformamide (10 mL) was stirred at 80°C for 10 h. The reaction mixture was poured into water and  
35 extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and

concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl [6-(2-amino-2-oxoethoxy)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.37 g, 78.7%) as crystals.

Melting point 180-181°C.

Elemental analysis for  $C_{25}H_{37}N_3O_6$

Calculated: C, 63.14; H, 7.84; N, 8.84.

10 Found: C, 62.90; H, 7.71; N, 8.98.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.95 (6H, d,  $J=6.6$  Hz), 1.04 (3H, t,  $J=7.3$  Hz), 1.46 (9H, s), 1.51-1.67 (2H, m), 1.80-1.94 (2H, m), 2.05-2.23 (2H, m), 3.84 (2H, t,  $J=6.6$  Hz), 3.98 (2H, d,  $J=7.2$  Hz), 4.51 (2H, d,  $J=5.6$  Hz), 4.62 (2H, s), 15 4.76 (1H, bs), 5.84 (1H, bs), 6.59 (1H, bs), 7.07-7.13 (2H, m), 8.37 (1H, d,  $J=9.2$  Hz).

(10) To a solution of tert-butyl [6-(2-amino-2-oxoethoxy)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.29 g, 0.6 mmol) in 20 ethyl acetate (5 mL) was added a solution of 4N hydrogen chloride in ethyl acetate (5 mL) and the obtained solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from 25 methanol - diisopropyl ether to give 2-[[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]oxy]acetamide hydrochloride (0.23 g, 92.0%) as crystals.

Melting point 248-250°C.

30 Elemental analysis for  $C_{20}H_{30}N_3O_4Cl \cdot 0.5H_2O$

Calculated: C, 57.07; H, 7.42; N, 9.98.

Found: C, 57.22; H, 7.67; N, 9.73.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.87 (6H, d,  $J=6.6$  Hz), 0.99 (3H, t,  $J=7.3$  Hz), 1.47 (9H, s), 1.47-1.65 (2H, m), 1.73-2.04 35 (3H, m), 3.88-3.95 (4H, m), 4.17 (2H, s), 4.64 (2H, s), 7.06 (1H, d,  $J=2.5$  Hz), 7.23 (1H, dd,  $J=2.5, 8.8$  Hz),

7.46 (1H, s), 7.73 (1H, s), 8.20 (1H, d, J=9.2 Hz), 8.62 (3H, s).

**Example 151**

(E)-3-[3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide hydrochloride

(1) To a solution of ethyl diethylphosphonoacetate (1.4 mL, 7 mmol) in N,N-dimethylformamide (30 mL) was added sodium hydride (0.28 g, 7 mmol) (60% in oil) and the mixture was stirred at room temperature for 10 min. To the obtained mixture was added a solution of tert-butyl (4-butoxy-6-formyl-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (3.01 g, 7 mmol) in N,N-dimethylformamide (10 mL) and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give ethyl (E)-3-(4-butoxy-3-[[tert-butoxycarbonyl]amino]methyl]-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl)-2-propenate (3.11 g, 88.9%) as crystals.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.96 (6H, d, J=6.6 Hz), 1.06 (3H, t, J=7.2 Hz), 1.37 (3H, t, J=7.2 Hz), 1.47 (9H, s), 1.53-1.68 (2H, m), 1.84-1.94 (2H, m), 2.12-2.22 (1H, m), 3.87 (2H, t, J=6.6 Hz), 3.99 (2H, d, J=7.5 Hz), 4.30 (2H, q, J=7.2 Hz), 4.52 (2H, d, J=5.7 Hz), 4.78 (1H, bs), 6.58 (1H, d, J=16.0 Hz), 7.65 (1H, dd, J=1.5, 8.1 Hz), 7.79 (1H, d, J=1.5 Hz), 7.79 (1H, d, J=16.0 Hz), 8.41 (1H, d, J=8.1 Hz).

(2) To a solution of ethyl (E)-3-(4-butoxy-3-[[tert-butoxycarbonyl]amino]methyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl)-2-propenate (1.00 g, 2 mmol) in tetrahydrofuran (10 mL) and ethanol (10 mL) was added 1N sodium hydroxide (4 mL). The obtained mixture was stirred at room temperature for 2 h. The reaction

- mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give (E)-3-(4-butoxy-3-[[tert-butoxycarbonyl]amino]methyl]-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl)-2-propenic acid (0.89 g, 94.7%) as crystals.
- 10 Melting point 207-209°C.  
Elemental analysis for  $C_{26}H_{36}N_2O_6$   
Calculated: C, 66.08; H, 7.68; N, 5.93.  
Found: C, 65.85; H, 7.52; N, 5.91.  
 $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.96 (6H, d,  $J=6.6$  Hz), 1.07 (3H, t,  $J=7.3$  Hz), 1.49 (9H, s), 1.49-1.69 (2H, m), 1.83-1.97 (2H, m), 2.05-2.24 (1H, m), 3.88 (2H, t,  $J=6.4$  Hz), 3.99 (2H, d,  $J=7.2$  Hz), 4.53 (2H, d,  $J=5.6$  Hz), 5.16 (1H, bs), 6.58 (1H, d,  $J=16.0$  Hz), 7.62 (1H, d,  $J=8.2$  Hz), 7.71 (1H, s), 7.84 (1H, d,  $J=16.0$  Hz), 8.36 (1H, d,  $J=8.2$  Hz).
- 20 (3) A solution of (E)-3-(4-butoxy-3-[[tert-butoxycarbonyl]amino]methyl]-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)-2-propenic acid (0.47 g, 1 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.38 g, 2 mmol) and 1-hydroxybenzotriazole ammonium salt (0.30 g, 2 mmol) in N,N-dimethylformamide (10 mL) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - n-hexane to give (E)-3-(4-butoxy-3-[[tert-butoxycarbonyl]amino]methyl]-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)-2-propenamide (0.41 g, 87.2%) as crystals.
- 35 Melting point 149-150°C.

Elemental analysis for  $C_{26}H_{37}N_3O_5 \cdot 0.5H_2O$

Calculated: C, 64.98; H, 7.97; N, 8.74.

Found: C, 64.71; H, 7.68; N, 8.56.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.96 (6H, d,  $J=6.6$  Hz), 1.01 (3H, t,  $J=7.4$  Hz), 1.47 (9H, s), 1.49-1.67 (2H, m), 1.81-1.95 (2H, m), 2.09-2.21 (1H, m), 3.86 (2H, t,  $J=6.5$  Hz), 3.99 (2H, d,  $J=7.2$  Hz), 4.52 (2H, d,  $J=5.6$  Hz), 4.95 (1H, bs), 5.86 (1H, bs), 6.01 (1H, bs), 6.60 (1H, d,  $J=16.2$  Hz), 7.58 (1H, d,  $J=8.5$  Hz), 7.71 (1H, s), 7.74 (1H, d,  $J=16.2$  Hz), 8.33 (1H, d,  $J=8.4$  Hz).

(4) To a solution of (E)-3-(4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)-2-propenamide (0.14 g, 0.3 mmol) in ethyl acetate (5 mL) was added a solution of 4N hydrogen chloride in ethyl acetate (5 mL) and the obtained solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol - diisopropyl ether to give (E)-3-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide hydrochloride (0.11 g, 91.7%) as crystals.

Melting point 223-225°C.

Elemental analysis for  $C_{21}H_{30}N_3O_3Cl \cdot 0.5H_2O$

Calculated: C, 60.49; H, 7.49; N, 10.08.

Found: C, 60.37; H, 7.77; N, 9.73.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.89 (6H, d,  $J=6.6$  Hz), 1.01 (3H, t,  $J=7.2$  Hz), 1.48-1.66 (2H, m), 1.82-2.08 (3H, m), 3.93-3.99 (4H, m), 4.18 (2H, d,  $J=4.8$  Hz), 6.84 (1H, d,  $J=16.1$  Hz), 7.28 (1H, bs), 7.64 (1H, d,  $J=16.1$  Hz), 7.76 (1H, bs), 7.80-7.87 (2H, m), 8.29 (1H, d,  $J=8.0$  Hz), 8.64 (3H, bs).

#### Example 152

(E)-3-[3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide

(1) To a suspension of (E)-3-[3-(aminomethyl)-4-butoxy-



2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide hydrochloride (2.04 g, 5 mmol) in water (20 mL) was added 1N sodium hydroxide (20 mL). The obtained mixture was stirred at room temperature for 10 min. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate to give (E)-3-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide (1.02 g, 85.0%) as crystals. Melting point 173-175°C.

Elemental analysis for  $C_{21}H_{29}N_3O_3$

Calculated: C, 67.90; H, 7.87; N, 11.31.

Found: C, 67.73; H, 7.90; N, 11.03.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.96 (6H, d,  $J=6.6$  Hz), 1.05 (3H, t,  $J=7.3$  Hz), 1.42 (2H, bs), 1.47-1.69 (2H, m), 1.81-1.95 (1H, m), 3.89 (2H, t,  $J=6.4$  Hz), 4.01 (2H, s), 4.10 (2H, d,  $J=7.4$  Hz), 5.89 (1H, bs), 6.04 (1H, bs), 6.65 (1H, d,  $J=15.6$  Hz), 7.62 (1H, dd,  $J=1.4, 8.4$  Hz), 7.76 (1H, d,  $J=1.4$  Hz), 7.78 (1H, d,  $J=15.6$  Hz), 8.39 (1H, d,  $J=8.4$  Hz).

Powder X-ray crystal diffraction data.

Diffraction angle:  $2\theta(^{\circ})$       spacing: d value  
(angstrom)

25	8.62	10.2
	9.98	8.86
	17.4	5.09
	23.0	3.87
30	21.9	4.06
	26.3	3.38
	24.2	3.68

#### Example 153

3-(Aminomethyl)-4-butoxy-2-isobutyl-6-(1,3-oxazol-5-yl)-1(2H)-isoquinolinone hydrochloride  
(1) A solution of tert-butyl (4-butoxy-6-formyl-2-

isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.34 g, 0.8 mmol), p-toluenesulfonylmethyl isocyanide (0.16 g, 0.8 mmol) and potassium carbonate (0.22 g, 1.6 mmol) in methanol (10 mL) was refluxed under heating for 30 min. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography and the precipitated crystals were recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl [4-butoxy-2-isobutyl-6-(1,3-oxazol-5-yl)-1-oxo-1,2-dihydro-3-isoquinolinyl]-methylcarbamate (0.34 g, 91.9%) as crystals.

Melting point 152-153°C.

Elemental analysis for  $C_{26}H_{35}N_3O_5$

Calculated: C, 66.50; H, 7.51; N, 8.95.

Found: C, 66.25; H, 7.57; N, 9.00.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.97 (6H, d,  $J=7.0$  Hz), 1.07 (3H, t,  $J=7.3$  Hz), 1.47 (9H, s), 1.55-1.73 (2H, m), 1.84-1.98 (2H, m), 2.12-2.26 (1H, m), 3.91 (2H, t,  $J=6.4$  Hz), 4.00 (2H, d,  $J=7.4$  Hz), 4.54 (2H, d,  $J=5.4$  Hz), 4.81 (1H, bs), 7.53 (1H, d,  $J=0.8$  Hz), 7.72-7.78 (1H, m), 7.97 (1H, s), 8.01 (1H, d,  $J=0.8$  Hz), 8.45 (1H, dd,  $J=1.4, 8.4$  Hz).

(2) To a solution of tert-butyl [4-butoxy-2-isobutyl-6-(1,3-oxazol-5-yl)-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.28 g, 0.6 mmol) in ethyl acetate (5 mL) was added a solution of 4N hydrogen chloride in ethyl acetate (5 mL) and the obtained solution was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol - diisopropyl ether to give 3-(aminomethyl)-4-butoxy-2-isobutyl-6-(1,3-oxazol-5-yl)-1(2H)-isoquinolinone hydrochloride (0.22 g, 91.7%) as crystals. Melting point 211-213°C.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.90 (6H, d, J=6.6 Hz), 1.03 (3H, t, J=7.3 Hz), 1.55-1.67 (2H, m), 1.84-1.93 (2H, m), 2.02-2.12 (1H, m), 3.96-4.01 (4H, m), 4.20 (2H, d, J=5.4 Hz), 8.00-8.02 (3H, m), 8.36 (1H, d, J=9.0 Hz), 8.64 (1H, s),  
5 8.82 (3H, bs).

#### Example 154

2-[[3-(Aminomethyl)-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]oxy]acetamide

(1) To a suspension of 4-benzyloxyphthalic anhydride  
10 (25.42 g, 100 mmol) in methanol (200 mL) was added 28% sodium methoxide methanol solution (21.22 g, 110 mmol) and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into 1N hydrochloric acid (150 mL) and extracted with ethyl acetate. The  
15 extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylformamide (200 mL) and methyl 2-(isobutylamino)acetate (17.42 g, 120 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (23.00  
20 g, 120 mmol) and 1-hydroxybenzotriazole (18.34 g, 120 mmol) were added, and the mixture was stirred at room temperature for 3 h. The reaction mixture was poured into water and extracted with ethyl acetate. The  
25 extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in methanol (50 mL) and a solution of 28% sodium methoxide methanol solution (38.59 g, 200 mmol) was added thereto. The mixture was  
30 stirred at room temperature for 1 h. The reaction mixture was poured into 1N hydrochloric acid (200 mL) and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The  
35 residue was purified by silica gel column chromatography and the component eluted earlier was concentrated to

give methyl 7-benzyloxy-4-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (4.76 g, 12.1%) as an oil.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.82 (6H, d, J=6.6 Hz), 1.78-1.87 (1H, m), 3.99 (3H, s), 4.39 (2H, d, J=7.5 Hz), 5.25 (2H, s), 7.25-7.48 (6H, m), 7.96-7.98 (1H, m), 8.10 (1H, d, J=8.7 Hz), 11.34 (1H, s).

The component eluted later was concentrated to give methyl 6-benzyloxy-4-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (21.41 g, 54.4%) as crystals.

Melting point 109-110°C.

Elemental analysis for C<sub>22</sub>H<sub>23</sub>NO<sub>5</sub>

Calculated: C, 69.28; H, 6.08; N, 3.67.

Found: C, 69.28; H, 5.93; N, 3.48.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.81 (6H, d, J=6.6 Hz), 1.66-1.85 (1H, m), 4.00 (3H, s), 4.35 (2H, d, J=7.5 Hz), 5.21 (2H, s), 7.31 (1H, dd, J=2.6, 8.8 Hz), 7.38-7.49 (5H, m), 7.60 (1H, d, J=2.6 Hz), 8.38 (1H, d, J=8.8 Hz), 11.12 (1H, s).

(2) To a solution of methyl 6-benzyloxy-4-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (7.86 g, 20 mmol) in N,N-dimethylformamide (100 mL) was added sodium hydride (0.96 g, 24 mmol) (60% in oil) at 0°C and the mixture was stirred at 0°C for 30 min. To the obtained mixture was added N-phenyltrifluoromethanesulfonimide (8.57 g, 24 mmol) and the mixture was stirred at room temperature for 3 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give methyl 6-benzyloxy-2-isobutyl-1-oxo-4-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinecarboxylate (10.50 g, 100%) as an oil.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.88 (6H, d, J=7.0 Hz), 1.92-2.05 (1H,

m), 3.99 (3H, s), 5.19 (2H, s), 7.23-7.48 (2H, m), 8.37 (1H, d,  $J=9.2$  Hz).

(3) A mixture of methyl 6-benzyloxy-2-isobutyl-1-oxo-4-trifluoromethanesulfonyloxy-1,2-dihydro-3-

5 isoquinolinecarboxylate (10.50 g, 20 mmol), 2-fluorophenylboronic acid (3.36 g, 24 mmol) and sodium carbonate (5.30 g, 50 mmol) in toluene (50 mL), ethanol (10 mL) and water (10 mL) was stirred under an argon atmosphere at room temperature for 30 min. To the  
10 obtained mixture was added

tetrakis(triphenylphosphine)palladium (1.16 g, 1 mmol) and the mixture was refluxed under heating under an argon atmosphere for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate.

15 After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give methyl 6-benzyloxy-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-  
20 dihydro-3-isoquinolinecarboxylate (6.06 g, 65.9%) as crystals.

Melting point: 106-107°C.

Elemental analysis for  $C_{28}H_{26}NO_4F$

Calculated: C, 73.19; H, 5.70; N, 3.05.

25 Found: C, 73.18; H, 5.83; N, 2.86.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.91 (3H, d,  $J=6.6$  Hz), 0.92 (3H, d,  $J=7.0$  Hz), 2.05-2.19 (1H, m), 3.47 (3H, s), 3.86 (1H, dd,  $J=7.6, 13.8$  Hz), 4.08 (1H, dd,  $J=7.6, 13.8$  Hz), 4.98 (2H, s), 6.50-6.52 (1H, m), 7.13-7.50 (10H, m), 8.43 (1H, d,  $J=8.8$  Hz).  
30

(4) To a solution of methyl 6-benzyloxy-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (0.46 g, 1 mmol) in methanol (30 mL) was added an aqueous solution (3 mL) of lithium  
35 hydroxide monohydrate (0.42 g, 10 mmol). The obtained mixture was refluxed under heating for 12 h. The

reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give 6-benzyloxy-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (0.41 g, 93.2%) as crystals.

10 Melting point 178-179°C.

Elemental analysis for  $C_{27}H_{24}NO_4F \cdot 0.25H_2O$

Calculated: C, 72.07; H, 5.49; N, 3.11.

Found: C, 72.28; H, 5.20; N, 2.80.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.85 (6H, d,  $J=6.8$  Hz), 2.09-2.23 (1H, m), 3.75-3.96 (2H, m), 4.38 (1H, bs), 4.98 (2H, s), 6.49-6.51 (1H, m), 7.10-7.48 (10H, m), 8.30 (1H, d,  $J=8.8$  Hz).

(5) To a solution of 6-benzyloxy-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (4.90 g, 11 mmol) in tetrahydrofuran (50 mL) were added oxalyl chloride (1.1 mL, 13.2 mmol) and N,N-dimethylformamide (3 drops), and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in tetrahydrofuran (30 mL). The obtained solution was added dropwise to a suspension of sodium tetrahydroborate (1.46 g, 38.5 mmol) in 1,2-dimethoxyethane (30 mL) at 0°C. The obtained mixture was stirred at 0°C for 1 h. The reaction mixture was poured into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give 6-benzyloxy-4-(2-fluorophenyl)-3-hydroxymethyl-2-isobutyl-1(2H)-isoquinolinone (4.38 g, 92.4%) as

crystals.

Melting point 191-192°C.

Elemental analysis for  $C_{27}H_{26}NO_3F \cdot 0.25H_2O$

Calculated: C, 74.38; H, 6.13; N, 3.21.

5 Found: C, 74.52; H, 6.20; N, 3.16.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.87 (6H, d,  $J=6.6$  Hz), 1.85 (1H, bs),  
2.18-2.32 (1H, m), 4.08-4.29 (2H, m), 4.44 (2H, s), 4.94  
(2H, s), 6.38 (1H, d,  $J=2.3$  Hz), 7.09 (1H, dd,  $J=2.3$ ,  
8.6 Hz), 7.18-7.36 (7H, m), 7.43-7.54 (1H, m), 8.36 (1H,  
10 d,  $J=8.6$  Hz).

(6) To a suspension of 6-benzyloxy-4-(2-fluorophenyl)-3-  
hydroxymethyl-2-isobutyl-1(2H)-isoquinolinone (4.31 g,  
10 mmol) in toluene (50 mL) was added thionyl chloride  
(1.5 mL, 20 mmol). The obtained mixture was refluxed  
15 under heating for 2 h. The reaction mixture was poured  
into saturated aqueous sodium hydrogencarbonate solution  
and extracted with ethyl acetate. The extract was  
washed with brine, dried over anhydrous magnesium  
sulfate and concentrated under reduced pressure to give  
20 6-benzyloxy-3-chloromethyl-4-(2-fluorophenyl)-2-  
isobutyl-1(2H)-isoquinolinone (4.29 g, 95.3%) as  
crystals.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.98 (3H, d,  $J=6.6$  Hz), 1.01 (3H, d,  
 $J=6.8$  Hz), 2.15-2.26 (1H, m), 3.94 (1H, dd,  $J=7.9$ , 13.1  
25 Hz), 4.31 (1H, d,  $J=12.4$  Hz), 4.35 (1H, dd,  $J=7.9$ , 13.1  
Hz), 4.43 (1H, d,  $J=12.4$  Hz), 4.95 (2H, s), 6.36-6.38  
(1H, m), 7.12-7.35 (9H, m), 7.45-7.56 (1H, m), 8.41 (1H,  
d,  $J=8.8$  Hz).

(7) A solution of 6-benzyloxy-3-chloromethyl-4-(2-  
30 fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone (4.27 g,  
9.5 mmol) and potassium phthalimide (2.65 g, 14.3 mmol)  
in *N,N*-dimethylformamide (100 mL) was stirred at room  
temperature for 6 h. The reaction mixture was poured  
into water and extracted with ethyl acetate. After  
35 washing the extract with water, the extract was dried  
over anhydrous magnesium sulfate and concentrated under

reduced pressure. The residue was purified by silica gel column chromatography to give 2-[[6-benzyloxy-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methyl]-1H-isoindole-1,3(2H)-dione (5.07 g, 95.3%) as an amorphous.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.00 (3H, d, J=6.6 Hz), 1.01 (3H, d, J=6.8 Hz), 2.12-2.27 (1H, m), 3.94 (1H, dd, J=7.3, 14.8 Hz), 4.33 (1H, dd, J=7.3, 13.9 Hz), 4.57 (1H, d, J=15.6 Hz), 4.92 (1H, d, J=15.6 Hz), 4.93 (2H, s), 6.34 (1H, d, J=2.6 Hz), 7.01-7.45 (10H, m), 7.66-7.76 (4H, m), 8.40 (1H, d, J=8.8 Hz).

(8) To a solution of 2-[[6-benzyloxy-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methyl]-1H-isoindole-1,3(2H)-dione (5.05 g, 9 mmol) in ethanol (50 mL) was added hydrazine monohydrate (1.3 mL, 27 mmol). The obtained mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (50 mL) and di-*t*-butyl dicarbonate (3.1 mL, 13.5 mmol) was added thereto. The obtained mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - *n*-hexane to give tert-butyl [6-benzyloxy-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (4.27 g, 89.5%) as crystals.

Melting point 138-139°C.

Elemental analysis for C<sub>32</sub>H<sub>35</sub>N<sub>2</sub>O<sub>4</sub>F

Calculated: C, 72.43; H, 6.65; N, 5.28.

Found: C, 72.27; H, 6.38; N, 5.22.



<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.99 (6H, d, J=7.0 Hz), 1.43 (9H, s), 2.16-2.30 (1H, m), 3.83-3.94 (1H, m), 3.99-4.38 (3H, m), 4.58 (1H, bs), 4.95 (2H, s), 6.33 (1H, d, J=2.4 Hz), 7.11 (1H, dd, J=2.4, 9.0 Hz), 7.16-7.38 (8H, m), 7.43-7.54 (1H, m), 8.39 (1H, d, J=9.0 Hz).

(9) A suspension of tert-butyl [6-benzyloxy-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (3.98 g, 7.5 mmol) and 5% palladium carbon (1.5 g) in ethanol (50 mL) was stirred under a hydrogen atmosphere at room temperature for 2 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran - diisopropyl ether to give tert-butyl [4-(2-fluorophenyl)-6-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (3.11 g, 94.2%) as crystals.

Melting point 163-164°C.

Elemental analysis for C<sub>25</sub>H<sub>29</sub>N<sub>2</sub>O<sub>4</sub>F 0.5H<sub>2</sub>O

Calculated: C, 66.80; H, 6.73; N, 6.23.

Found: C, 66.80; H, 6.93; N, 6.28.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.96 (6H, d, J=6.6 Hz), 1.42 (9H, s), 2.11-2.28 (1H, m), 3.82-3.92 (1H, m), 4.02-4.21 (2H, m), 4.28-4.38 (1H, m), 4.60 (1H, bs), 6.37 (1H, d, J=2.2 Hz), 7.08 (1H, dd, J=2.2, 8.8 Hz), 7.13-7.23 (4H, m), 7.34-7.47 (1H, m), 8.28 (1H, d, J=8.8 Hz).

(10) A solution of tert-butyl [4-(2-fluorophenyl)-6-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.44 g, 1 mmol), 2-iodoacetamide (0.37 g, 2 mmol) and 1,8-diazabicyclo[5.4.0]-7-undecene (0.30 mL, 2 mmol) in N,N-dimethylformamide (10 mL) was stirred at 80°C for 10 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by

silica gel column chromatography to give tert-butyl [6-(2-amino-2-oxoethoxy)-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.30 g, 61.2%) as crystals.

5 Melting point 186-188°C.

Elemental analysis for  $C_{27}H_{32}N_3O_5F \cdot 0.25H_2O$

Calculated: C, 64.59; H, 6.52; N, 8.37.

Found: C, 64.74; H, 6.32; N, 7.97.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (3H, d,  $J=7.0$  Hz), 1.00 (3H, d,  $J=6.8$  Hz), 1.43 (9H, s), 2.15-2.32 (1H, m), 3.85-4.00 (4H, m), 4.35 (2H, s), 4.59 (1H, bs), 5.70 (1H, bs), 6.29 (1H, d,  $J=2.4$  Hz), 6.50 (1H, bs), 7.07 (1H, dd,  $J=2.4, 9.0$  Hz), 7.21-7.37 (3H, m), 7.46-7.58 (1H, m), 8.44 (1H, d,  $J=9.0$  Hz).

15 (11) To a solution of tert-butyl [6-(2-amino-2-oxoethyl)-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.25 g, 0.5 mmol) in ethyl acetate (5 mL) was added a solution of 4N hydrogen chloride in ethyl acetate (5 mL), and the  
20 obtained solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure. The residue was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried  
25 over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 2-[[3-(aminomethyl)-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]oxy]acetamide (0.02 g, 10.0%) as an  
30 amorphous.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.00 (3H, d,  $J=6.6$  Hz), 1.02 (3H, d,  $J=6.6$  Hz), 1.66 (2H, bs), 2.18-2.32 (1H, m), 4.07-4.28 (3H, m), 4.35 (2H, s), 5.77 (1H, bs), 6.27 (1H, d,  $J=2.6$  Hz), 6.51 (1H, bs), 7.05 (1H, dd,  $J=2.6, 8.8$  Hz), 7.22-7.35 (3H, m), 7.45-7.56 (1H, m), 8.44 (1H, d,  $J=8.8$  Hz).

Example 155

3-(Aminomethyl)-4-(2-fluorophenyl)-2-isobutyl-1(2H)-  
isoquinolinone-6-carboxamide hydrochloride

(1) To a solution of tert-butyl [4-(2-fluorophenyl)-6-  
hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-

5 isoquinolinyl)methylcarbamate (Example 8(9)) (2.42 g,  
5.5 mmol) in N,N-dimethylformamide (30 mL) was added  
sodium hydride (0.33 g, 8.3 mmol) (60% in oil) at 0°C and  
the mixture was stirred at 0°C for 30 min. To the  
obtained mixture was added N-

10 phenyltrifluoromethanesulfonimide (2.97 g, 8.3 mmol) and  
the mixture was stirred at room temperature for 1 h.

The reaction mixture was poured into water and extracted  
with ethyl acetate. After washing the extract with  
water, the extract was dried over anhydrous magnesium

15 sulfate and concentrated under reduced pressure. The  
residue was purified by silica gel column chromatography  
to give tert-butyl [4-(2-fluorophenyl)-2-isobutyl-1-oxo-  
6-trifluoromethanesulfonyloxy-1,2-dihydro-3-  
isoquinolinyl]methylcarbamate (2.91 g, 92.4%) as an  
20 amorphous.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.00 (3H, d, J=6.6 Hz), 1.01 (3H, d,  
J=7.0 Hz), 1.46 (9H, s), 2.17-2.31 (1H, m), 3.89-3.99  
(1H, m), 4.07-4.27 (2H, m), 4.33-4.44 (1H, m), 4.59 (1H,  
bs), 6.79 (1H, d, J=2.2 Hz), 7.21-7.44 (1H, m), 7.48-  
25 7.60 (1H, m), 8.57 (1H, d, J=8.8 Hz).

(2) A mixed solution of tert-butyl [4-(2-fluorophenyl)-  
2-isobutyl-1-oxo-6-trifluoromethanesulfonyloxy-1,2-  
dihydro-3-isoquinolinyl]methylcarbamate (2.86 g, 5 mmol),  
1,1'-bis(diphenylphosphino)ferrocene (0.14 g, 0.25 mmol),  
30 triethylamine (0.77 mL, 5.5 mmol) and palladium acetate  
(56 mg, 0.25 mmol) in tetrahydrofuran (20 mL) and  
methanol (20 mL) was stirred with heating at 100°C under  
a carbon monoxide atmosphere at 5 atm for 1 h. The  
reaction mixture was poured into water and extracted  
35 with ethyl acetate. After washing the extract with  
water, the extract was dried over anhydrous magnesium

sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give methyl 3-[[[(tert-butoxycarbonyl)amino]methyl]-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-

5 isoquinolinecarboxylate (2.23 g, 92.5%) as crystals.

Melting point 180-181°C.

Elemental analysis for  $C_{27}H_{31}N_2O_5F$

Calculated: C, 67.20; H, 6.48; N, 5.81.

Found: C, 66.95; H, 6.55; N, 5.75.

10  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.00 (3H, d,  $J=6.6$  Hz), 1.01 (3H, d,  $J=6.6$  Hz), 1.43 (9H, s), 2.19-2.33 (1H, m), 3.86 (3H, s), 3.89-4.43 (4H, m), 4.62 (1H, bs), 7.23-7.38 (3H, m), 7.47-7.58 (1H, m), 7.46 (1H, d,  $J=1.5$  Hz), 8.06 (1H, dd,  $J=1.5$ , 8.4 Hz), 8.53 (1H, d,  $J=8.4$  Hz).

15 (3) To a solution of methyl 3-[[[(tert-butoxycarbonyl)amino]methyl]-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylate (1.93 g, 4 mmol) in tetrahydrofuran (10 mL) and methanol (10 mL) was added 1N sodium hydroxide (8 mL). The  
20 obtained mixture was stirred at room temperature for 1 h.

The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under

25 reduced pressure. The obtained crystals were recrystallized from ethyl acetate - isopropyl ether to give 3-[[[(tert-butoxycarbonyl)amino]methyl]-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid (1.77 g, 94.7%) as crystals.

30 Melting point 213-214°C.

Elemental analysis for  $C_{26}H_{29}N_2O_5F$

Calculated: C, 66.65; H, 6.24; N, 5.98.

Found: C, 66.51; H, 6.50; N, 5.99.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.00 (3H, d,  $J=6.8$  Hz), 1.01 (3H, d,  $J=6.6$  Hz), 1.45 (9H, s), 2.19-2.32 (1H, m), 4.84 (1H, bs), 7.22-7.34 (3H, m), 7.46-7.57 (1H, m), 7.65 (1H, s),  
35

8.05 (1H, d, J=8.4 Hz), 8.51 (1H, d, J=8.4 Hz).

(4) A solution of 3-[[[tert-butoxycarbonyl)amino]methyl]-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid  
5 (0.70 g, 1.5 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.58 g, 3 mmol) and 1-hydroxybenzotriazole ammonium salt (0.46 g, 3 mmol) in N,N-dimethylformamide (10 mL) was stirred at room temperature for 3 h. The reaction mixture was  
10 poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran-diisopropyl ether to give 3-  
15 [[[(tert-butoxycarbonyl)amino]methyl]-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide (0.67 g, 95.7%) as crystals.

Melting point 232-233°C.

Elemental analysis for  $C_{26}H_{30}N_3O_4F$

20 Calculated: C, 66.79; H, 6.47; N, 8.99.

Found: C, 66.39; H, 6.75; N, 8.93.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (3H, d, J=6.6 Hz), 1.01 (3H, d, J=6.6 Hz), 1.44 (9H, s), 2.22-2.30 (1H, m), 3.92-4.19 (3H, m), 4.32-4.40 (1H, m), 4.69 (1H, bs), 5.78 (1H, bs),  
25 6.10 (1H, bs), 7.23-7.35 (3H, m), 7.40 (1H, d, J=1.5 Hz), 7.47-7.54 (1H, m), 7.77 (1H, dd, J=1.5, 8.4 Hz), 8.49 (1H, d, J=8.4 Hz).

(5) To a solution of 3-[[[tert-butoxycarbonyl)amino]methyl]-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide  
30 (0.37 g, 0.8 mmol) in ethyl acetate (5 mL) was added a solution of 4N hydrogen chloride in ethyl acetate (5 mL) and the obtained solution was stirred at room temperature for 1 h. The reaction mixture was  
35 concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol.

- diethyl ether to give 3-(aminomethyl)-4-(2-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carboxamide hydrochloride (0.30 g, 93.8%) as crystals. Melting point 216-218°C.

5 Elemental analysis for  $C_{21}H_{23}N_3O_2ClF \cdot 2H_2O$

Calculated: C, 57.34; H, 6.19; N, 9.55.

Found: C, 57.41; H, 5.93; N, 9.71.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.92 (3H, d,  $J=6.6$  Hz), 0.93 (3H, d,  $J=6.6$  Hz), 2.01-2.16 (1H, m), 3.62-3.80 (1H, m), 4.02-  
10 4.23 (3H, m), 7.43-7.66 (6H, m), 8.03 (1H, d,  $J=8.4$  Hz), 8.21 (1H, bs), 8.38 (1H, d,  $J=8.4$  Hz), 8.72 (3H, bs).

#### Example 156

3-(Aminomethyl)-4-(2-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carbonitrile hydrochloride

15 (1) A solution of 3-[(tert-butoxycarbonyl)amino]methyl]-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide (Example 10 (4)) (0.23 g, 0.5 mmol) and cyanuric chloride (0.28 g, 1.5 mmol) in N,N-dimethylformamide (10  
20 mmol) was stirred at 0°C for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced  
25 pressure. The residue was recrystallized from ethyl acetate - n-hexane to give tert-butyl [6-cyano-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.19 g, 86.4%) as crystals.

Melting point 191-192°C.

30 Elemental analysis for  $C_{26}H_{28}N_3O_3F$

Calculated: C, 69.47; H, 6.28; N, 9.35.

Found: C, 69.37; H, 6.42; N, 9.24.

$^1H$ -NMR(CDCl $_3$ )  $\delta$ : 1.00 (3H, d,  $J=6.6$  Hz), 1.01 (3H, d,  $J=7.0$  Hz), 1.43 (9H, s), 2.18-2.32 (1H, m), 3.89-4.05  
35 (1H, m), 4.07-4.44 (3H, m), 4.58 (1H, bs), 7.20-7.40 (4H, m), 7.50-7.61 (1H, m), 7.67 (1H, dd,  $J=1.6, 8.2$  Hz),

8.56 (1H, d, J=8.2 Hz).

(2) To a solution of tert-butyl [6-cyano-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.13 g, 0.3 mmol) in ethyl acetate (5 mL) was added a solution of 4N hydrogen chloride in ethyl acetate (5 mL) and the obtained solution was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol-diethyl ether to give 3-(aminomethyl)-4-(2-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carbonitrile hydrochloride (0.11 g, 91.7%) as crystals. Melting point 228-230°C.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.92 (3H, d, J=6.6 Hz), 0.94 (3H, d, J=6.6 Hz), 1.99-2.19 (1H, m), 3.76-3.83 (1H, m), 3.96-4.22 (3H, m), 7.30 (1H, d, J=1.4 Hz), 7.41-7.72 (4H, m), 7.99 (1H, dd, J=1.4, 8.4 Hz), 8.49 (1H, d, J=8.4 Hz), 8.74 (3H, bs).

#### Example 157

2-[[3-(Aminomethyl)-4-(3-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]oxy]acetamide hydrochloride (1) A mixture of methyl 6-benzyloxy-2-isobutyl-1-oxo-4-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinecarboxylate (10.26 g, 20 mmol), 3-fluorophenylboronic acid (3.36 g, 24 mmol) and sodium carbonate (5.30 g, 50 mmol) in toluene (50 mL), ethanol (10 mL) and water (10 mL) was stirred under an argon atmosphere at room temperature for 30 min. To the obtained mixture was added tetrakis(triphenylphosphine)palladium (1.16 g, 1 mmol) and the mixture was refluxed under heating under an argon atmosphere for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by

silica gel column chromatography to give methyl 6-benzyloxy-4-(3-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (6.31 g, 68.7%) as crystals.

5 Melting point 127-128°C.

Elemental analysis for  $C_{26}H_{26}NO_4F$

Calculated: C, 73.19; H, 5.70; N, 3.05.

Found: C, 73.03; H, 5.63; N, 2.77.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.91 (6H, d,  $J=7.0$  Hz), 2.04-2.19 (1H, m), 3.50 (3H, s), 3.8-4.00 (2H, m), 4.99 (2H, s), 6.57 (1H, d,  $J=2.4$  Hz), 6.96-7.21 (4H, m), 7.24-7.46 (6H, m), 8.43 (1H, d,  $J=8.8$  Hz).

(2) To a solution of methyl 6-benzyloxy-4-(3-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (5.97 g, 13 mmol) in tetrahydrofuran (50 mL) and methanol (50 mL) was added an aqueous solution (10 mL) of lithium hydroxide monohydrate (1.64 g, 39 mmol). The obtained mixture was refluxed under heating for 12 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (50 mL), and oxalyl chloride (1.0 mL, 12 mmol) and N,N-dimethylformamide (3 drops) were added thereto. The mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in tetrahydrofuran (30 mL). The obtained solution was added dropwise to a suspension of sodium tetrahydroborate (1.32 g, 35 mmol) in 1,2-dimethoxyethane (30 mL) at 0°C. The obtained mixture was stirred at 0°C for 1 h. The reaction mixture was poured into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under



reduced pressure. The residue was purified by silica gel column chromatography to give 6-benzyloxy-4-(3-fluorophenyl)-3-hydroxymethyl-2-isobutyl-1(2H)-isoquinolinone (1.39 g, 32.2%) as crystals.

5 Melting point 146-146.5°C.

Elemental analysis for  $C_{27}H_{26}NO_3F$

Calculated: C, 75.15; H, 6.07; N, 3.25.

Found: C, 74.87; H, 6.06; N, 3.12.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.94 (6H, d,  $J=6.6$  Hz), 2.11-2.28 (1H, m), 2.58 (1H, bs), 4.16 (2H, d,  $J=7.6$  Hz), 4.41 (2H, d,  $J=5.8$  Hz), 4.91 (2H, s), 6.31 (1H, d,  $J=2.2$  Hz), 6.95-7.37 (9H, m), 7.44-7.52 (1H, m), 8.25 (1H, d,  $J=8.8$  Hz).

(3) To a suspension of 6-benzyloxy-4-(3-fluorophenyl)-3-hydroxymethyl-2-isobutyl-1(2H)-isoquinolinone (3.88 g, 9 mmol) in toluene (30 mL) was added thionyl chloride (1.3 mL, 18 mmol). The obtained mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 6-benzyloxy-3-chloromethyl-4-(3-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone (3.71 g, 91.8%) as an oil.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (6H, d,  $J=6.6$  Hz), 2.13-2.31 (1H, m), 4.14 (2H, d,  $J=7.2$  Hz), 4.35 (2H, s), 4.96 (2H, s), 6.37 (1H, d,  $J=2.2$  Hz), 6.98-7.32 (9H, m), 7.42-7.53 (1H, m), 8.40 (1H, d,  $J=8.8$  Hz).

(4) A solution of 6-benzyloxy-3-chloromethyl-4-(3-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone (3.60 g, 8 mmol) and potassium phthalimide (2.22 g, 12 mmol) in N,N-dimethylformamide (30 mL) was stirred at room temperature for 6 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were

recrystallized from ethyl acetate - diisopropyl ether to give 2-[[6-benzyloxy-4-(3-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methyl]-1H-isoindole-1,3(2H)-dione (3.95 g, 88.2%) as crystals.

5 <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.98 (6H, d, J=6.6 Hz), 2.10-2.27 (1H, m), 4.03 (2H, d, J=4.4 Hz), 4.75 (2H, s), 4.92 (2H, s), 6.32 (1H, d, J=2.6 Hz), 6.98-7.14 (4H, m), 7.21-7.40 (6H, m), 7.68-7.78 (4H, m), 8.38 (1H, d, J=8.8 Hz).

(5) To a solution of 2-[[6-benzyloxy-4-(3-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methyl]-1H-isoindole-1,3(2H)-dione (3.92 g, 7 mmol) in ethanol (50 mL) was added hydrazine monohydrate (1.0 mL, 21 mmol). The obtained mixture was refluxed under heating for 2 h.

The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (30 mL) and di-*t*-butyl dicarbonate (2.4 mL, 10.5 mmol) was added. The obtained mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [(6-benzyloxy-4-(3-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methyl]carbamate (3.47 g, 93.5%) as crystals.

30 Melting point 180-181°C.

Elemental analysis for C<sub>32</sub>H<sub>35</sub>N<sub>2</sub>O<sub>4</sub>F

Calculated: C, 72.43; H, 6.65; N, 5.28.

Found: C, 72.30; H, 6.48; N, 5.32.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.98 (6H, d, J=6.6 Hz), 1.43 (9H, s), 2.15-2.28 (1H, m), 4.02 (2H, d, J=7.4 Hz), 4.16 (2H, d, J=5.0 Hz), 4.94 (2H, s), 6.31 (1H, d, J=2.6 Hz), 6.89-

7.35 (9H, m), 7.41-7.52 (1H, m), 8.36 (1H, d, J=8.8 Hz).

(6) A suspension of tert-butyl [6-benzyloxy-4-(3-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (3.18 g, 6 mmol) and 5% palladium carbon (1.0 g) in tetrahydrofuran (20 mL) and ethanol (20 mL) was stirred under a hydrogen atmosphere at room temperature for 2 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - n-hexane to give tert-butyl [4-(3-fluorophenyl)-6-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (2.54 g, 96.2%) as crystals.

Melting point 161-163°C.

Elemental analysis for  $C_{25}H_{29}N_2O_4F$

Calculated: C, 68.16; H, 6.64; N, 6.36.

Found: C, 67.91; H, 6.89; N, 6.38.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.96 (6H, d, J=6.6 Hz), 1.42 (9H, s), 2.14-2.24 (1H, m), 4.01 (2H, d, J=5.7 Hz), 4.18 (2H, d, J=4.5 Hz), 4.52 (1H, bs), 6.34 (1H, d, J=2.1 Hz), 6.94-7.13 (4H, m), 7.38-7.46 (1H, m), 7.87 (1H, bs), 8.26 (1H, d, J=8.4 Hz).

(7) A solution of tert-butyl [(4-(3-fluorophenyl)-6-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.44 g, 1 mmol), 2-iodoacetamide (0.37 g, 2 mmol) and 1,8-diazabicyclo[5.4.0]-7-undecene (0.3 mL, 2 mmol) in N,N-dimethylacetamide (10 mL) was stirred at 70°C for 10 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [6-(2-amino-2-oxoethoxy)-4-(3-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.21 g, 42.9%) as crystals.

Melting point 241-242°C.

Elemental analysis for  $C_{27}H_{32}N_3O_5F \cdot 0.25H_2O$

Calculated: C, 64.59; H, 6.52; N, 8.37.

Found: C, 64.61; H, 6.66; N, 8.07.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.99 (6H, d, J=6.6 Hz), 1.43 (9H, s), 2.19-2.34 (1H, m), 4.04 (2H, d, J=7.0 Hz), 4.35 (2H, s), 4.86 (1H, bs), 6.15 (1H, bs), 6.31 (1H, d, J=2.6 Hz), 6.59 (1H, bs), 6.99-7.25 (4H, m), 7.45-7.54 (1H, m), 8.42 (1H, d, J=9.2 Hz).

(8) To a solution of tert-butyl [6-(2-amino-2-oxoethoxy)-4-(3-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.15 g, 0.3 mmol) in ethyl acetate (5 mL) was added a solution of 4N hydrogen chloride in ethyl acetate (5 mL), and the obtained solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and crystallized from ethyl acetate - diisopropyl ether to give 2-[[3-(aminomethyl)-4-(3-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]oxy]acetamide hydrochloride (0.12 g, 92.3%) as crystals.

Melting point 209-210°C.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.91 (6H, d, J=6.6 Hz), 1.99-2.18 (1H, m), 3.84 (2H, bs), 3.94-4.08 (2H, m), 4.39 (2H, s), 6.29 (1H, d, J=2.2 Hz), 7.18-7.41 (5H, m), 8.27 (1H, d, J=9.2 Hz), 8.59 (3H, bs).

#### Example 158

3-(Aminomethyl)-4-(3-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carboxamide hydrochloride

(1) To a solution of tert-butyl [4-(3-fluorophenyl)-6-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (Example 11 (6)) (1.76 g, 4 mmol) in N,N-dimethylformamide (20 mL) was added sodium hydride (0.19 g, 4.8 mmol) (60% in oil) at 0°C and the mixture was stirred at 0°C for 30 min. To the obtained mixture was added N-

- phenyltrifluoromethanesulfonimide (1.71 g, 4.8 mmol) and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with
- 5 water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [4-(3-fluorophenyl)-2-isobutyl-1-oxo-6-trifluoromethanesulfonyloxy-1,2-dihydro-3-
- 10 isoquinolinyl]methylcarbamate (2.30 g, 100%) as an oil.  
<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.99 (6H, d, J=6.6 Hz), 1.43 (9H, s), 2.14-2.28 (1H, m), 4.08 (2H, d, J=9.0 Hz), 4.23 (2H, d, J=5.6 Hz), 4.50 (1H, bs), 6.80 (1H, d, J=2.6 Hz), 6.96-7.08 (2H, m), 7.18-7.59 (3H, m), 8.55 (1H, d, J=8.8 Hz).
- 15 (2) A mixed solution of tert-butyl [4-(3-fluorophenyl)-2-isobutyl-1-oxo-6-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinyl]methylcarbamate (2.29 g, 4 mmol), 1,1'-bis(diphenylphosphino)ferrocene (0.11 g, 0.2 mmol), triethylamine (0.6 mL, 4.4 mmol) and palladium acetate
- 20 (45 mg, 0.2 mmol) in tetrahydrofuran (20 mL) and methanol (20 mL) was stirred with heating at 100°C under a carbon monoxide atmosphere at 5 atm for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with
- 25 water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give methyl 3-[[[(tert-butoxycarbonyl)amino]methyl]-4-(3-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-
- 30 isoquinolinecarboxylate (1.76 g, 91.2%) as crystals. Melting point 206-208°C.  
Elemental analysis for C<sub>27</sub>H<sub>31</sub>N<sub>2</sub>O<sub>5</sub>F  
Calculated: C, 67.20; H, 6.48; N, 5.81.  
Found: C, 66.96; H, 6.63; N, 5.59.
- 35 <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.00 (6H, d, J=6.6 Hz), 1.44 (9H, s), 2.18-2.30 (1H, m), 3.87 (3H, s), 4.08 (2H, d, J=7.2 Hz),

4.21 (2H, d, J=5.1 Hz), 4.54 (1H, bs), 6.99-7.08 (2H, m), 7.18-7.27 (1H, m), 7.62 (1H, d, J=1.2 Hz), 8.04 (1H, dd, J=1.2, 8.4 Hz), 8.50 (1H, d, J=8.4 Hz).

(3) To a solution of methyl 3-[[tert-

5 butoxycarbonyl)amino]methyl]-4-(3-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylate (1.45 g, 3 mmol) in tetrahydrofuran (10 mL) and methanol (10 mL) was added 1N sodium hydroxide (6 mL). The obtained mixture was stirred at room temperature for 2 h.

10 The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was crystallized from

15 ethyl acetate - n-hexane to give 3-[[tert-butoxycarbonyl)amino]methyl]-4-(3-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid (1.34 g, 95.7%) as crystals.

Melting point 206-207°C.

20 Elemental analysis for  $C_{26}H_{29}N_2O_5F$

Calculated: C, 66.65; H, 6.24; N, 5.98.

Found: C, 66.39; H, 6.33; N, 5.63.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (6H, d, J=6.6 Hz), 1.48 (9H, s), 2.10-2.29 (1H, m), 4.05 (2H, d, J=7.4 Hz), 4.17 (2H, d, J=4.4 Hz), 5.49 (1H, bs), 7.05-7.27 (3H, m), 7.44-7.58 (2H, m), 7.86-7.90 (1H, m), 8.36 (1H, d, J=8.4 Hz).

25 (4) A solution of 3-[[tert-butoxycarbonyl)amino]methyl]-4-(3-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid (1.17 g, 2.5 mmol), 1-ethyl-3-(3-

30 dimethylaminopropyl)carbodiimide hydrochloride (0.96 g, 5 mmol) and 1-hydroxybenzotriazole ammonium salt (0.76 g, 5 mmol) in N,N-dimethylformamide (10 mL) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous

magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran - diisopropyl ether to give 3-  
5 2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide (0.81 g, 69.8%) as crystals.

Melting point 147-149°C.

Elemental analysis for  $C_{26}H_{30}N_3O_4F \cdot 0.5H_2O$

Calculated: C, 65.53; H, 6.56; N, 8.82.

10 Found: C, 65.91; H, 6.44; N, 8.87.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.00 (6H, d,  $J=7.0$  Hz), 1.44 (9H, s),  
2.14-2.30 (1H, m), 4.07 (2H, d,  $J=7.4$  Hz), 4.19 (2H, d,  
 $J=5.6$  Hz), 4.73 (1H, bs), 5.77 (1H, bs), 6.11 (1H, bs),  
6.98-7.25 (3H, m), 7.37 (1H, d,  $J=1.8$  Hz), 7.45-7.56 (1H,  
15 m), 7.72 (1H, dd,  $J=1.8, 8.4$  Hz), 8.42 (1H, d,  $J=8.4$  Hz).

(5) To a solution of 3-[[[(tert-butoxycarbonyl)amino]methyl]-4-(3-fluorophenyl)-2-  
isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide  
(0.28 g, 0.6 mmol) in ethyl acetate (5 mL) was added a  
20 solution of 4N hydrogen chloride in ethyl acetate (5 mL)  
and the obtained solution was stirred at room  
temperature for 1 h. The reaction mixture was  
concentrated under reduced pressure, and the  
precipitated crystals were recrystallized from methanol  
25 - diethyl ether to give 3-(aminomethyl)-4-(3-  
fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-  
carboxamide hydrochloride (0.22 g, 91.7%) as crystals.  
Melting point 292-293°C.

Elemental analysis for  $C_{21}H_{23}N_3O_2ClF \cdot 0.5H_2O$

30 Calculated: C, 61.09; H, 5.86; N, 10.18.

Found: C, 60.79; H, 6.09; N, 10.04.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.93 (6H, d,  $J=6.6$  Hz), 2.02-2.19 (1H,  
m), 3.87 (2H, bs), 4.00-4.20 (2H, m), 7.26-7.45 (4H, m),  
7.58-7.69 (2H, m), 8.01 (1H, dd,  $J=1.6, 8.4$  Hz), 8.19  
35 (1H, bs), 8.38 (1H, d,  $J=8.4$  Hz), 8.61 (3H, bs).

Example 159

(E)-3-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-2-propenamide hydrochloride

(1) To a solution of 3-[[tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxylic acid (6.31 g, 14 mmol) and N-methylmorpholine (1.8 mL, 16.8 mmol) in tetrahydrofuran (50 mL) was added ethyl chloroformate (1.6 mL, 16.8 mmol) at 0°C and the mixture was stirred at 0°C for 10 min. To the obtained mixture were added sodium tetrahydroborate (1.59 g, 42 mmol) and methanol (5 mL) and the mixture was stirred at 0°C for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The precipitated crystals were recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl (6-hydroxymethyl-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (4.73 g, 77.4%) as crystals.

Melting point 169-170°C.

Elemental analysis for  $C_{26}H_{32}N_2O_4$

Calculated: C, 71.53; H, 7.39; N, 6.42.

Found: C, 71.25; H, 7.49; N, 6.35.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.99 (6H, d,  $J=6.6$  Hz), 1.43 (9H, s), 2.04 (1H, bs), 2.16-2.29 (1H, m), 4.06 (2H, d,  $J=7.4$  Hz), 4.18 (2H, d,  $J=5.4$  Hz), 4.64 (2H, d,  $J=6.0$  Hz), 4.66 (1H, bs), 6.89 (1H, s), 7.22-7.27 (2H, m), 7.49-7.54 (4H, m), 8.38 (1H, d,  $J=8.0$  Hz).

(2) To a solution of tert-butyl (6-hydroxymethyl-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (4.58 g, 10.5 mmol) in tetrahydrofuran (50 mL) was added manganese dioxide (13.7 g) and the mixture was stirred at room temperature for 12 h. Manganese dioxide was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography



to give tert-butyl (6-formyl-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinoliny) methylcarbamate (4.12 g, 90.4%) as crystals.

Melting point 183-184°C.

5 Elemental analysis for  $C_{26}H_{30}N_2O_4$

Calculated: C, 71.87; H, 6.96; N, 6.45.

Found: C, 71.79; H, 6.84; N, 6.36.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.02 (6H, d,  $J=6.6$  Hz), 1.43 (9H, s),  
2.19-2.32 (1H, m), 4.10 (2H, d,  $J=7.4$  Hz), 4.24 (2H, d,  
10  $J=5.6$  Hz), 4.51 (1H, bs), 7.26-7.30 (2H, m), 7.44 (1H, d,  
 $J=1.4$  Hz), 7.51-7.59 (3H, m), 7.92 (1H, dd,  $J=1.4, 8.2$   
Hz), 8.59 (1H, d,  $J=8.2$  Hz), 9.95 (1H, s).

(3) To a solution of ethyl diethylphosphonoacetate (1.0 mL, 5 mmol) in N,N-dimethylformamide (20 mL) was added  
15 sodium hydride (0.20 g, 5 mmol) (60% in oil), and the mixture was stirred at room temperature for 10 min. To the obtained mixture was added a solution of tert-butyl (6-formyl-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinoliny) methylcarbamate (2.17 g, 5 mmol) in N,N-  
20 dimethylformamide (20 mL) and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced  
25 pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give ethyl (E)-3-[3-[[tert-butoxycarbonyl]amino]methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinoliny]-2-propionate (2.03 g, 71.7%) as an amorphous.

30 Melting point 147-148°C.

Elemental analysis for  $C_{30}H_{36}N_2O_5$

Calculated: C, 71.40; H, 7.19; N, 5.55.

Found: C, 71.37; H, 7.15; N, 5.43.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.01 (6H, d,  $J=7.0$  Hz), 1.31 (3H, t,  
35  $J=7.3$  Hz), 1.43 (9H, s), 2.18-2.31 (1H, m), 4.08 (2H, d,  $J=7.4$  Hz), 4.13-4.28 (4H, m), 4.53 (1H, bs), 6.37 (1H, d,

J=16.2 Hz), 7.00 (1H, d, J=1.4 Hz), 7.18-7.28 (2H, m), 7.44-7.67 (5H, m), 8.44 (1H, d, J=8.0 Hz).

(4) To a solution of ethyl (E)-3-[3-[[tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-2-propenate (0.70 g, 1.4 mmol) in tetrahydrofuran (10 mL) and ethanol (10 mL) was added 1N sodium hydroxide (3 mL). The obtained mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - n-hexane to give (E)-3-[3-[[tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-2-propenic acid (0.56 g, 84.8%) as crystals.

Melting point 172-173°C.

Elemental analysis for  $C_{28}H_{32}N_2O_5$

Calculated: C, 70.27; H, 7.16; N, 5.85.

Found: C, 70.08; H, 6.80; N, 5.65.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (6H, d, J=6.6 Hz), 1.48 (9H, s), 2.16-2.24 (1H, m), 4.06 (2H, d, J=7.2 Hz), 4.15 (2H, d, J=4.0 Hz), 5.62 (1H, bs), 6.27 (1H, d, J=16.0 Hz), 6.82 (1H, s), 7.33-7.40 (3H, m), 7.48-7.58 (3H, m), 8.28 (1H, d, J=8.8 Hz).

(5) A solution of (E)-3-[3-[[tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-2-propenic acid (0.33 g, 0.7 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.27 g, 1.4 mmol) and 1-hydroxybenzotriazole ammonium salt (0.21 g, 1.4 mmol) in N,N-dimethylformamide (10 mL) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous

magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give (E)-3-[3-  
5 [[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-2-propenamide (0.31 g, 93.9%) as crystals.

Melting point 146-147°C.

Elemental analysis for  $C_{28}H_{33}N_3O_4 \cdot 0.25H_2O$

Calculated: C, 70.05; H, 7.03; N, 8.75.

10 Found: C, 70.08; H, 7.09; N, 8.64.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.00 (6H, d,  $J=6.6$  Hz), 1.44 (9H, s),  
2.16-2.24 (1H, m), 4.07 (2H, d,  $J=7.4$  Hz), 4.19 (2H, d,  
 $J=5.6$  Hz), 4.96 (1H, bs), 5.75 (1H, bs), 6.38 (1H, d,  
 $J=15.6$  Hz), 6.94 (1H, s), 7.26-7.30 (2H, m), 7.40-7.56  
15 (5H, m), 8.29 (1H, d,  $J=8.4$  Hz).

(6) A solution of (E)-3-[3-[[ (tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-4-phenyl-  
1,2-dihydro-6-isoquinolinyl]-2-propenamide (0.24 g, 0.5  
mmol) in ethyl acetate (5 mL) was added a solution of 4N  
20 hydrogen chloride in ethyl acetate (5 mL), and the  
obtained solution was stirred at room temperature for 2  
h. The reaction mixture was concentrated under reduced  
pressure, and the precipitated crystals were  
recrystallized from methanol - diisopropyl ether to give  
25 (E)-3-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-  
dihydro-6-isoquinolinyl]-2-propenamide hydrochloride  
(0.20 g, 95.2%) as crystals.

Melting point 223-225°C.

Elemental analysis for  $C_{23}H_{26}N_3O_2Cl \cdot 1.5H_2O$

30 Calculated: C, 62.93; H, 6.66; N, 9.57.

Found: C, 63.15; H, 6.66; N, 9.34.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.92 (6H, d,  $J=6.9$  Hz), 2.06-2.16 (1H,  
m), 3.87 (2H, d,  $J=4.8$  Hz), 4.08 (2H, s), 6.56 (1H, d,  
 $J=16.0$  Hz), 7.19 (1H, bs), 7.31 (1H, d,  $J=16.0$  Hz),  
35 7.42-7.44 (2H, m), 7.54-7.63 (3H, m), 7.69 (1H, bs),  
7.78 (1H, dd,  $J=1.2, 8.8$  Hz), 8.35 (1H, d,  $J=8.8$  Hz),

8.62 (3H, bs).

# Example 160

(E)-3-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-2-propenamide

- 5 (1) (E)-3-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-2-propenamide hydrochloride (Example 159 (6)) (0.13 g, 0.3 mmol) was dissolved in water (10 mL) and saturated aqueous potassium carbonate solution (10 mL) was added. The mixture was extracted  
10 with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The precipitated crystals were recrystallized from ethyl acetate - diisopropyl ether to give (E)-3-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-  
15 1,2-dihydro-6-isoquinolinyl]-2-propenamide (0.06 g, 54.5%) as crystals.

Melting point 228-230°C.

- <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.00 (6H, d, J=7.0 Hz), 1.47 (2H, bs),  
2.19-2.33 (1H, m), 3.69 (2H, s), 4.22 (2H, d, J=7.0 Hz),  
20 5.70 (2H, bs), 6.43 (1H, d, J=15.8 Hz), 6.99 (1H, d, J=1.5 Hz), 7.25-7.29 (2H, m), 7.47-7.55 (4H, m), 7.58 (1H, dd, J=1.5, 8.4 Hz), 8.44 (1H, d, J=8.4 Hz).

Recrystallization from ethanol - ethyl acetate gave crystals in a different crystal form.

- 25 Melting point 275-276°C

Powder X-ray crystal diffraction data

Diffraction angle: 2θ(°)                      spacing: d value  
(angstrom)

- |    |      |      |
|----|------|------|
|    | 8.66 | 10.2 |
| 30 | 13.6 | 6.50 |
|    | 17.5 | 5.07 |
|    | 21.4 | 4.15 |

# Example 161

2-[[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]oxy]acetamide hydrochloride

- 35 (1) To a suspension of 4-benzyloxyphthalic anhydride

(2.54 g, 10 mmol) in ethanol (30 mL) was added 20% sodium ethoxide ethanol solution (3.74 g, 11 mmol) and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into 1N hydrochloric acid (150 mL) and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in N,N-dimethylformamide (200 mL) and tert-butyl 2-(isobutylamino)acetate (2.25 g, 12 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (2.30 g, 12 mmol) and 1-hydroxybenzotriazole (1.84 g, 12 mmol) were added and the mixture was stirred at room temperature for 3 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in ethanol (30 mL) and a solution (6.80 g, 20 mmol) of 20% sodium ethoxide in ethanol was added thereto. The mixture was stirred at room temperature for 1 h. The reaction mixture was poured into 1N hydrochloric acid (20 mL) and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography and the component eluted earlier was concentrated to give tert-butyl 7-benzyloxy-4-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (0.40 g, 9.5%) as an oil.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.82 (6H, d, J=6.6 Hz), 1.78-1.87 (1H, m), 3.99 (3H, s), 4.39 (2H, d, J=7.5 Hz), 5.25 (2H, s), 7.25-7.48 (6H, m), 7.96-7.98 (1H, m), 8.10 (1H, d, J=8.7 Hz), 11.34 (1H, s).

The component eluted later was concentrated to give tert-butyl 6-benzyloxy-4-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (1.51 g, 35.7%) as

crystals.

Melting point 133-134°C.

Elemental analysis for  $C_{25}H_{29}NO_5$

Calculated: C, 70.90; H, 6.90; N, 3.31.

5 Found: C, 70.84; H, 6.85; N, 3.11.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.81 (6H, d,  $J=6.6$  Hz), 1.64 (9H, s),  
1.73-1.84 (1H, m), 4.38 (2H, d,  $J=7.4$  Hz), 5.21 (2H, s),  
7.29 (1H, dd,  $J=2.4, 8.8$  Hz), 7.35-7.51 (5H, m), 7.58  
(1H, d,  $J=2.4$  Hz), 8.37 (1H, d,  $J=8.8$  Hz), 11.17 (1H, s).

10 (2) To a solution of tert-butyl 6-benzyloxy-4-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (6.35 g, 15 mmol) in N,N-dimethylformamide (50 mL) was added sodium hydride (0.72 g, 18 mmol) (60% in oil) at 0°C and the mixture was stirred at 0°C for 30 min. To

15 the obtained mixture was added N-phenyltrifluoromethanesulfonimide (6.43 g, 18 mmol) and the mixture was stirred at room temperature for 2 h.

The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with

20 water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl 6-benzyloxy-2-isobutyl-1-oxo-4-trifluoromethanesulfonyloxy-1,2-dihydro-3-

25 isoquinolinecarboxylate (6.62 g, 81.2%) as an oil.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.89 (6H, d,  $J=6.6$  Hz), 1.64 (9H, s),  
2.04-2.15 (1H, m), 4.03 (2H, d,  $J=7.4$  Hz), 5.18 (2H, s),  
7.20-7.56 (7H, m), 8.34 (1H, d,  $J=9.2$  Hz).

(3) A mixed solution of tert-butyl 6-benzyloxy-2-isobutyl-1-oxo-4-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinecarboxylate (6.52 g, 12 mmol),  
30 phenylboronic acid (1.76 g, 14.4 mmol) and sodium carbonate (3.18 g, 30 mmol) in toluene (50 mL), ethanol (10 mL) and water (10 mL) was stirred under an argon atmosphere at room temperature for 10 min. To the  
35 obtained mixture was added tetrakis(triphenylphosphine)-

palladium (0.69 g, 0.6 mmol) and the mixture was refluxed under heating under an argon atmosphere for 10 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract  
5 with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl 6-benzyloxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-  
10 isoquinolinecarboxylate (5.01 g, 86.4%) as crystals. Melting point 138-139°C.

Elemental analysis for  $C_{31}H_{33}NO_4$

Calculated: C, 76.99; H, 6.88; N, 2.90.

Found: C, 77.04; H, 6.80; N, 2.70.

15  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.94 (6H, d,  $J=6.9$  Hz), 1.15 (9H, s), 2.17-2.27 (1H, m), 3.98 (2H, d,  $J=7.5$  Hz), 4.95 (2H, s), 6.53 (1H, d,  $J=2.4$  Hz), 7.13 (1H, dd,  $J=2.4, 8.8$  Hz), 7.25-7.36 (6H, m), 7.40-7.45 (4H, m), 8.41 (1H, d,  $J=8.8$  Hz).

20 (4) A solution of tert-butyl 6-benzyloxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinecarboxylate (9.03 g, 25 mmol) in trifluoroacetic acid (30 mL) was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the obtained  
25 crystals were recrystallized from ethyl acetate - diisopropyl ether to give 6-benzyloxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinecarboxylic acid (3.50 g, 82.0%) as crystals.

30  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.85 (6H, d,  $J=6.6$  Hz), 2.09-2.14 (1H, m), 3.83 (2H, d,  $J=7.5$  Hz), 4.96 (2H, s), 6.58 (1H, d,  $J=2.4$  Hz), 7.09-7.44 (11H, m), 8.29 (1H, d,  $J=8.7$  Hz).

(5) To a solution of 6-benzyloxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinecarboxylic acid (3.42 g, 8 mmol) in tetrahydrofuran (30 mL) were added oxalyl  
35 chloride (0.84 mL, 9.6 mmol) and N,N-dimethylformamide (3 drops), and the mixture was stirred at room

temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in tetrahydrofuran (20 mL). The obtained solution was added dropwise to a suspension of sodium tetrahydroborate (1.06 g, 28 mmol) in 1,2-dimethoxyethane (20 mL) at 0°C. The obtained mixture was stirred at 0°C for 1 h. The reaction mixture was poured into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran - diisopropyl ether to give 6-benzyloxy-3-hydroxymethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (2.92 g, 88.5%) as crystals.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.96 (6H, d, J=6.6 Hz), 2.16-2.40 (2H, m), 4.18 (2H, d, J=7.5 Hz), 4.43 (2H, s), 4.89 (2H, s), 6.37 (1H, d, J=2.4 Hz), 7.00 (1H, dd, J=2.4, 9.0 Hz), 7.21-7.34 (7H, m), 7.44-7.52 (3H, m), 8.30 (1H, d, J=9.0 Hz).

(6) To a suspension of 6-benzyloxy-3-hydroxymethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (2.89 g, 7 mmol) in toluene (30 mL) was added thionyl chloride (1.0 mL, 14 mmol). The obtained mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 6-benzyloxy-3-chloromethyl-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (2.61 g, 86.4%) as crystals.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.00 (6H, d, J=7.0 Hz), 2.12-2.31 (1H, m), 4.16 (2H, d, J=7.4 Hz), 4.37 (2H, s), 4.93 (2H, s), 6.41 (1H, d, J=2.3 Hz), 7.13 (1H, dd, J=2.3, 9.0 Hz), 7.19-7.35 (7H, m), 7.45-7.54 (3H, m), 8.41 (1H, d, J=9.0 Hz).

(7) A solution of 6-benzyloxy-3-chloromethyl-2-isobutyl-



4-phenyl-1(2H)-isoquinolinone (2.59 g, 6 mmol) and potassium phthalimide (1.67 g, 9 mmol) in N,N-dimethylformamide (30 mL) was stirred at room temperature for 6 h. The reaction mixture was poured  
5 into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to  
10 give 2-[(6-benzyloxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione (3.04 g, 93.5%) as crystals.

Melting point 113-114°C.

Elemental analysis for  $C_{35}H_{30}N_2O_4 \cdot 0.25H_2O$

15 Calculated: C, 76.83; H, 5.62; N, 5.12.

Found: C, 76.68; H, 5.79; N, 4.93.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (6H, d,  $J=6.4$  Hz), 2.14-2.28 (1H, m), 4.04 (2H, d,  $J=8.4$  Hz), 4.76 (2H, s), 4.91 (2H, s), 6.36 (1H, d,  $J=2.6$  Hz), 7.10 (1H, dd,  $J=2.6, 8.8$  Hz),  
20 7.20-7.39 (10H, m), 7.66-7.76 (4H, m), 8.39 (1H, d,  $J=8.8$  Hz).

(8) To a solution of 2-[(6-benzyloxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methyl]-1H-isoindole-1,3(2H)-dione (2.98 g, 5.5 mmol) in ethanol (30 mL) was  
25 added hydrazine monohydrate (0.8 mL, 16.5 mmol). The obtained mixture was refluxed under heating for 1 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried  
30 over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL) and di-t-butyl dicarbonate (1.9 mL, 8.3 mmol) was added thereto. The obtained mixture was stirred at room temperature for 1 h. The reaction  
35 mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over

anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl (6-benzyloxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (2.29 g, 81.2%) as crystals.

Melting point 141-142°C.

Elemental analysis for  $C_{32}H_{35}N_2O_4$

Calculated: C, 74.97; H, 7.08; N, 5.46.

10 Found: C, 74.60; H, 7.13; N, 5.45.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (6H, d,  $J=7.0$  Hz), 1.42 (9H, s), 2.16-2.30 (1H, m), 4.03 (2H, d,  $J=7.4$  Hz), 4.17 (2H, d,  $J=5.6$  Hz), 4.45 (1H, bs), 4.92 (2H, s), 6.35 (1H, d,  $J=2.4$  Hz), 7.09 (1H, dd,  $J=2.4, 9.0$  Hz), 7.17-7.37 (7H, m), 7.47-7.52 (3H, m), 8.38 (1H, d,  $J=9.0$  Hz).

15 (9) A suspension of tert-butyl (6-benzyloxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (2.05 g, 4 mmol) and 5% palladium carbon (0.6 g) in tetrahydrofuran (10 mL) and ethanol (10 mL) was stirred under a hydrogen atmosphere at room temperature for 2 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl (6-hydroxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (1.56 g, 92.3%) as crystals.

Melting point 218-219°C.

Elemental analysis for  $C_{25}H_{30}N_2O_4$

30 Calculated: C, 71.07; H, 7.16; N, 6.63.

Found: C, 70.85; H, 7.10; N, 6.62.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.97 (6H, d,  $J=6.8$  Hz), 1.42 (9H, s), 2.14-2.24 (1H, m), 4.02 (2H, d,  $J=7.2$  Hz), 4.18 (2H, d,  $J=5.4$  Hz), 4.47 (1H, bs), 6.33 (1H, d,  $J=2.4$  Hz), 7.03 (1H, dd,  $J=2.4, 8.8$  Hz), 7.20-7.27 (2H, m), 7.43-7.46 (3H, m), 7.97 (1H, bs), 8.30 (1H, d,  $J=8.8$  Hz).

(10) A solution of tert-butyl (6-hydroxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.63 g, 1.5 mmol), 2-iodoacetamide (0.43 g, 2.3 mmol) and 1,8-diazabicyclo[5.4.0]-7-undecene (0.34 mL, 2.3 mmol) in N,N-dimethylformamide (10 mL) was stirred at 80°C for 10 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl 6-(2-amino-2-oxoethoxy)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.32 g, 44.4%) as crystals.

Melting point 226-227°C.

Elemental analysis for  $C_{27}H_{33}N_3O_5$

Calculated: C, 67.62; H, 6.94; N, 8.76.

Found: C, 67.36; H, 6.73; N, 8.60.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.89 (6H, d,  $J=6.6$  Hz), 1.38 (9H, s), 2.07-2.21 (1H, m), 3.88 (2H, d,  $J=6.6$  Hz), 3.95 (2H, d,  $J=4.0$  Hz), 4.34 (2H, s), 6.30 (1H, d,  $J=2.4$  Hz), 7.13 (1H, dd,  $J=2.4, 8.8$  Hz), 7.34-7.52 (8H, m), 8.24 (1H, d,  $J=8.8$  Hz).

(11) To a solution of tert-butyl [6-(2-amino-2-oxoethoxy)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.24 g, 0.5 mmol) in ethyl acetate (5 mL) was added a solution of 4N hydrogen chloride in ethyl acetate (5 mL) and the obtained solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol-diethyl ether to give 2-[[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]oxy]acetamide hydrochloride (0.19 g, 95.0%) as crystals.

Melting point 185-186°C.

Elemental analysis for  $C_{22}H_{26}N_3O_3Cl \cdot 0.5H_2O$

Calculated: C, 62.23; H, 6.44; N, 9.75.

Found: C, 62.18; H, 6.40; N, 9.89.

$^1\text{H-NMR}$ (DMSO- $d_6$ )  $\delta$ : 0.91 (6H, d,  $J=6.6$  Hz), 2.01-2.18 (1H, m), 3.37 (2H, bs), 3.85 (2H, bs), 4.05 (2H, d,  $J=6.8$  Hz),  
5 4.36 (2H, s), 6.30 (1H, d,  $J=2.0$  Hz), 7.19 (1H, dd,  $J=2.0, 8.8$  Hz), 7.36-7.40 (2H, m), 7.52-7.58 (3H, m),  
8.28 (1H, d,  $J=8.8$  Hz), 8.55 (3H, s).

#### Example 162

2-[[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-  
10 dihydro-6-isoquinolinyl]oxy]acetamide  
(1) To a solution of tert-butyl [6-(2-amino-2-oxoethoxy)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.38 g, 0.8 mmol) in ethyl acetate (5 mL) was added a solution of 4N hydrogen  
15 chloride in ethyl acetate (5 mL) and the obtained solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was suspended in 1N aqueous sodium hydroxide solution. The suspension was stirred at room  
20 temperature for 10 min, and the reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The precipitated crystals were recrystallized  
25 from ethyl acetate - diisopropyl ether to give 2-[[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]oxy]acetamide (0.19 g, 63.3%) as crystals. Melting point 161-163°C.

Elemental analysis for  $\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_3 \cdot 0.25\text{H}_2\text{O}$

30 Calculated: C, 68.82; H, 6.69; N, 10.94.

Found: C, 69.02; H, 6.71; N, 10.80.

$^1\text{H-NMR}$ ( $\text{CDCl}_3$ )  $\delta$ : 0.99 (6H, d,  $J=7.0$  Hz), 1.29 (2H, bs), 2.18-3.66 (2H, s), 4.19 (2H, d,  $J=7.4$  Hz), 4.32 (2H, s), 5.81 (1H, bs), 6.30 (1H, d,  $J=2.4$  Hz), 6.51 (1H, bs),  
35 7.03 (1H, dd,  $J=2.4, 8.8$  Hz), 7.24-7.29 (2H, m), 7.44-7.56 (3H, m), 8.43 (1H, d,  $J=8.8$  Hz), 8.55 (3H, s).

**Example 163**

(E)-3-[3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide hydrochloride

- (1) To a solution of 4-butoxy-3-[[tert-butoxycarbonyl)amino]methyl]-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid (4.60 g, 10 mmol) and N-methylmorpholine (1.3 mL, 12 mmol) in tetrahydrofuran (30 mL) was added ethyl chloroformate (1.2 mL, 12 mmol) at 0°C and the mixture was stirred at 0°C for 10 min. To the obtained mixture were added sodium tetrahydroborate (1.13 g, 30 mmol) and methanol (5 mL), and the mixture was stirred at 0°C for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The precipitated crystals were recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl (4-butoxy-6-hydroxymethyl-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (2.89 g, 64.8%) as crystals.

Melting point 92-93°C.

Elemental analysis for  $C_{25}H_{38}N_2O_5$

Calculated: C, 67.24; H, 8.58; N, 6.27.

Found: C, 67.09; H, 8.43; N, 6.25.

- $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.98 (9H, s), 1.01 (3H, t, J=7.4 Hz), 1.46-1.63 (11H, m), 1.77-1.92 (2H, m), 2.80 (1H, bs), 3.85 (2H, t, J=6.8 Hz), 4.14 (2H, bs), 4.56 (2H, d, J=5.0 Hz), 4.82 (2H, s), 5.15 (1H, bs), 7.42 (1H, d, J=8.4 Hz), 7.53 (1H, s), 8.19 (1H, d, J=8.4 Hz).

- (2) To a solution of tert-butyl (4-butoxy-2-cyclopropylmethyl-6-formyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (2.27 g, 6.2 mmol) in tetrahydrofuran (30 mL) was added manganese dioxide (8.1 g) and the mixture was stirred at room temperature for 12 h. Manganese dioxide was filtered off and the mother liquor was concentrated under reduced pressure. The

residue was purified by silica gel column chromatography to give tert-butyl (4-butoxy-6-formyl-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (2.52 g, 91.6%) as crystals.

5 Melting point 149-150°C.

Elemental analysis for  $C_{25}H_{38}N_2O_5 \cdot 0.25H_2O$

Calculated: C, 66.87; H, 8.19; N, 6.24.

Found: C, 67.09; H, 8.15; N, 6.05.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.01 (9H, s), 1.06 (3H, t,  $J=7.4$  Hz),

10 1.45 (9H, s), 1.52-1.71 (2H, m), 1.84-1.98 (2H, m), 3.91 (2H, t,  $J=6.4$  Hz), 4.18 (2H, bs), 4.61 (2H, d,  $J=5.4$  Hz), 4.72 (1H, bs), 7.96 (1H, dd,  $J=1.7, 8.4$  Hz), 7.53 (1H, d,  $J=1.7$  Hz), 8.55 (1H, d,  $J=8.4$  Hz), 10.19 (1H, s).

(3) To a solution of ethyl diethylphosphonoacetate (1.1 mL, 5.5 mmol) in *N,N*-dimethylformamide (30 mL) was added

15 sodium hydride (0.22 g, 5.5 mmol) (60% in oil), and the mixture was stirred at room temperature for 10 min. To the obtained mixture was added a solution of tert-butyl (4-butoxy-6-formyl-2-neopentyl-1-oxo-1,2-dihydro-3-

20 isoquinolinyl)methylcarbamate (2.45 g, 5.5 mmol) in *N,N*-dimethylformamide (10 mL) and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous

25 magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give ethyl (E)-3-[4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl]-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propionate (2.03 g, 71.7%) as

30 an amorphous.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.00 (9H, s), 1.06 (3H, t,  $J=7.4$  Hz),

1.37 (3H, t,  $J=7.2$  Hz), 1.45 (9H, s), 1.51-1.66 (2H, m), 1.82-1.93 (2H, m), 3.88 (2H, t,  $J=6.6$  Hz), 4.14 (2H, bs), 4.30 (2H, q,  $J=7.2$  Hz), 4.58 (2H, d,  $J=5.2$  Hz), 4.71 (1H,

35 bs), 6.58 (1H, d,  $J=16.2$  Hz), 7.65 (1H, dd,  $J=1.6, 8.4$  Hz), 7.77 (1H, d,  $J=1.6$  Hz), 7.79 (1H, d,  $J=16.2$  Hz),

8.39 (1H, d, J=8.4 Hz).

(4) To a solution of ethyl (E)-3-[4-butoxy-3-[[tert-butoxycarbonyl)amino]methyl]-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenate (0.67g, 1.3 mmol) in tetrahydrofuran (5 mL) and ethanol (5 mL) was added 1N sodium hydroxide (3 mL). The obtained mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - n-hexane to give (E)-3-[4-butoxy-3-[[tert-butoxycarbonyl)amino]methyl]-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenic acid (0.53 g, 84.1%) as crystals.

Melting point 138-139°C.

Elemental analysis for  $C_{27}H_{38}N_2O_6$

Calculated: C, 66.64; H, 7.87; N, 5.76.

Found: C, 66.57; H, 7.84; N, 5.57.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.99 (9H, s), 1.07 (3H, t, J=7.3 Hz), 1.48 (9H, s), 1.49-1.67 (2H, m), 1.83-1.94 (2H, m), 3.88 (2H, t, J=6.6 Hz), 4.14 (2H, bs), 4.59 (2H, d, J=4.8 Hz), 5.32 (1H, bs), 6.57 (1H, d, J=15.7 Hz), 7.58 (1H, d, J=8.5 Hz), 7.68 (1H, s), 7.83 (1H, d, J=15.7 Hz), 8.29 (1H, d, J=8.5 Hz).

(5) A solution of (E)-3-[4-butoxy-3-[[tert-butoxycarbonyl)amino]methyl]-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenic acid (0.34 g, 0.7 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.27 g, 1.4 mmol) and 1-hydroxybenzotriazole ammonium salt (0.21 g, 1.4 mmol) in N,N-dimethylformamide (10 mL) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous

magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give (E)-3-[4-butoxy-3-[[tert-butoxycarbonyl]amino]methyl]-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide (0.29 g, 87.9%) as crystals.

Melting point 121-122°C.

Elemental analysis for  $C_{27}H_{39}N_3O_5 \cdot 0.5H_2O$

Calculated: C, 65.56; H, 8.15; N, 8.50.

10 Found: C, 66.18; H, 8.06; N, 8.59.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (9H, s), 1.05 (3H, t,  $J=7.2$  Hz), 1.46 (9H, s), 1.53-1.65 (2H, m), 1.83-1.93 (2H, m), 3.88 (2H, t,  $J=6.5$  Hz), 4.18 (2H, bs), 4.58 (2H, d,  $J=4.8$  Hz), 4.92 (1H, bs), 5.74 (1H, bs), 5.91 (1H, bs), 6.60 (1H, d,  $J=15.6$  Hz), 7.58 (1H, dd,  $J=1.5, 8.4$  Hz), 7.73 (1H, d,  $J=1.5$  Hz), 7.75 (1H, d,  $J=15.6$  Hz), 8.31 (1H, d,  $J=8.4$  Hz).

(6) To a solution of (E)-3-[4-butoxy-3-[[tert-butoxycarbonyl]amino]methyl]-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide (0.24 g, 0.5 mmol) in ethyl acetate (5 mL) was added a solution of 4N hydrogen chloride in ethyl acetate (5 mL) and the obtained solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol - diethyl ether to give (E)-3-[3-(aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide hydrochloride (0.19 g, 90.5%) as crystals.

30 Melting point 187-188°C.

Elemental analysis for  $C_{22}H_{32}N_3O_3Cl \cdot 0.75H_2O$

Calculated: C, 60.68; H, 7.75; N, 9.65.

Found: C, 60.53; H, 7.74; N, 9.73.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.91 (9H, s), 1.01 (3H, t,  $J=7.3$  Hz), 1.52-1.63 (2H, m), 1.82-1.93 (2H, m), 3.96 (2H, t,  $J=6.3$  Hz), 4.12 (2H, bs), 4.24 (2H, bs), 4.91 (1H, bs), 6.84



(1H, d, J=15.8 Hz), 7.29 (1H, bs), 7.63 (1H, d, J=15.8 Hz), 7.81 (1H, d, J=8.4 Hz), 7.87 (1H, bs), 8.29 (1H, d, J=8.4 Hz), 8.58 (3H, bs).

**Example 164**

5 2-[[3-(Aminomethyl)-2-isobutyl-1-oxo-4-(4,4,4-trifluorobutoxy)-1,2-dihydro-6-isoquinolinyl]oxy]acetamide hydrochloride

(1) A solution of 4-benzyloxyphthalic anhydride (4.07 g, 16 mmol) and ethyl 2-(isobutylamino)acetate (2.86 g, 18  
10 mmol) in tetrahydrofuran (30 mL) was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced  
15 pressure. The residue was dissolved in N,N-dimethylformamide (30 mL), and potassium carbonate (2.21 g, 16 mmol) and ethyl iodide (1.5 mL, 19.2 mmol) were added thereto. The mixture was stirred at room temperature for 3 h. The reaction mixture was poured  
20 into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in ethanol (50 mL), and a solution (10.9 g, 32 mmol) of 20% sodium ethoxide  
25 in ethanol was added thereto. The mixture was stirred at room temperature for 1 h. The reaction mixture was poured into 1N hydrochloric acid (70 mL) and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated  
30 under reduced pressure. The residue was purified by silica gel column chromatography and the component eluted earlier was concentrated to give ethyl 7-benzyloxy-4-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (4.21 g, 66.6%) as an oil.  
35 <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.82 (6H, d, J=6.6 Hz), 1.45 (3H, t, J=7.1 Hz), 1.77-1.91 (1H, m), 4.42-4.52 (4H, m), 7.31-

7.58 (6H, s), 7.97 (1H, d, J=2.6 Hz), 8.10 (1H, d, J=8.8 Hz), 11.45 (1H, s).

The component eluted later was concentrated to give ethyl 6-benzyloxy-4-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (0.80 g, 12.7%) as crystals.

Melting point 92-93°C.

Elemental analysis for  $C_{23}H_{25}NO_5$

Calculated: C, 69.86; H, 6.37; N, 3.54.

10 Found: C, 69.68; H, 6.20; N, 3.51.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.81 (6H, d, J=6.6 Hz), 1.46 (3H, t, J=7.2 Hz), 1.73-1.87 (1H, m), 4.39 (2H, d, J=7.2 Hz), 4.48 (2H, q, J=7.2 Hz), 5.21 (2H, s), 7.28-7.49 (6H, m), 7.60 (1H, d, J=2.6 Hz), 8.38 (1H, d, J=8.8 Hz), 11.23 (1H, s).

(2) To a solution of ethyl 6-benzyloxy-4-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (5.93 g, 15 mmol), 4,4,4-trifluorobutanol (2.31 g, 18 mmol) and tributylphosphine (7.5 mL, 30 mmol) in tetrahydrofuran (50 mL) was added 1,1'-(azodicarbonyl)dipiperidine (7.57 g, 30 mmol) and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to give ethyl 6-benzyloxy-2-isobutyl-1-oxo-4-(4,4,4-trifluorobutoxy)-1,2-dihydro-3-isoquinolinecarboxylate (6.71 g, 88.5%) as an oil.

25  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.89 (6H, d, J=6.6 Hz), 1.43 (3H, t, J=7.2 Hz), 1.90-2.37 (5H, m), 3.83-3.92 (4H, m), 4.43 (2H, q, J=7.2 Hz), 5.22 (2H, s), 7.03 (1H, d, J=2.4 Hz), 7.21 (1H, dd, J=2.4, 9.0 Hz), 7.33-7.46 (5H, m), 8.37 (1H, d, J=9.0 Hz).

(3) To a solution of ethyl 6-benzyloxy-2-isobutyl-1-oxo-4-(4,4,4-trifluorobutoxy)-1,2-dihydro-3-isoquinolinecarboxylate (6.57 g, 13 mmol) in ethanol (50 mL) was added an aqueous solution (20 mL) of sodium

hydroxide (2.08 g, 52 mmol). The obtained mixture was refluxed under heating for 12 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was  
5 washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - n-hexane to give 6-benzyloxy-2-isobutyl-1-oxo-4-(4,4,4-trifluorobutoxy)-1,2-dihydro-3-  
10 isoquinolinecarboxylic acid (4.89 g, 78.7%) as crystals. Melting point 130-131°C.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.85 (6H, d, J=6.4 Hz), 1.92-2.39 (5H, m), 3.89-3.93 (4H, m), 5.16 (2H, s), 6.79 (1H, d, J=2.6 Hz), 7.71 (1H, dd, J=2.6, 8.8 Hz), 7.32-7.41 (5H, m),  
15 8.18 (1H, d, J=8.8 Hz).

(4) 6-Benzyloxy-2-isobutyl-1-oxo-4-(4,4,4-trifluorobutoxy)-1,2-dihydro-3-isoquinolinecarboxylic acid (4.77 g, 10 mmol) was dissolved in tetrahydrofuran (50 mL), and oxalyl chloride (1.1 mL, 12 mmol) and N,N-dimethylformamide (3 drops) were added. The mixture was  
20 stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in tetrahydrofuran (20 mL). The obtained solution was added dropwise to a suspension of  
25 sodium tetrahydroborate (1.32 g, 35 mmol) in 1,2-dimethoxyethane (50 mL) at 0°C. The obtained mixture was stirred at 0°C for 1 h. The reaction mixture was poured into 1N hydrochloric acid and extracted with ethyl  
30 acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - n-hexane to give 6-benzyloxy-3-hydroxymethyl-2-isobutyl-4-(4,4,4-trifluorobutoxy)-1(2H)-isoquinolinone (4.02 g, 84.6%) as  
35 crystals. Melting point 112-113°C.

Elemental analysis for  $C_{25}H_{28}NO_4F_3$

Calculated: C, 65.67; H, 5.94; N, 2.95.

Found: C, 65.77; H, 6.21; N, 3.03.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.91 (6H, d,  $J=6.6$  Hz), 1.97-2.43 (5H, m), 2.56 (1H, bs), 3.83 (2H, t,  $J=6.2$  Hz), 4.03 (2H, d,  $J=7.4$  Hz), 4.76 (2H, d,  $J=5.6$  Hz), 5.20 (2H, s), 6.94 (1H, d,  $J=2.2$  Hz), 7.12 (1H, dd,  $J=2.2, 8.8$  Hz), 7.30-7.45 (5H, m), 8.27 (1H, d,  $J=8.8$  Hz).

(5) To a solution of 6-benzyloxy-3-hydroxymethyl-2-isobutyl-4-(4,4,4-trifluorobutoxy)-1(2H)-isoquinolinone (3.80 g, 8 mmol) in toluene (30 mL) was added thionyl chloride (1.2 mL, 16 mmol). The obtained mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 6-benzyloxy-3-chloromethyl-2-isobutyl-4-(4,4,4-trifluorobutoxy)-1(2H)-isoquinolinone (3.42 g, 88.8%) as an oil.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.95 (6H, d,  $J=6.6$  Hz), 2.00-2.46 (5H, m), 3.91 (2H, t,  $J=6.2$  Hz), 4.04 (2H, d,  $J=7.6$  Hz), 4.76 (2H, s), 5.23 (2H, s), 7.02 (1H, d,  $J=2.6$  Hz), 7.12-7.46 (6H, m), 8.38 (1H, d,  $J=8.8$  Hz).

(6) A solution of 6-benzyloxy-3-chloromethyl-2-isobutyl-4-(4,4,4-trifluorobutoxy)-1(2H)-isoquinolinone (3.37 g, 7 mmol) and potassium phthalimide (1.94 g, 10.5 mmol) in *N,N*-dimethylformamide (30 mL) was stirred at room temperature for 6 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, and the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - *n*-hexane to give 2-[[6-benzyloxy-2-isobutyl-1-oxo-4-(4,4,4-trifluorobutoxy)-1,2-dihydro-3-isoquinolinyl]methyl]-1H-

isoindole-1,3(2H)-dione (3.91 g, 94.4%) as crystals.

Melting point 131-132°C.

Elemental analysis for  $C_{33}H_{31}N_2O_5F_3$

Calculated: C, 66.88; H, 5.27; N, 4.73.

5 Found: C, 67.25; H, 5.21; N, 4.84.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.95 (6H, d,  $J=6.6$  Hz), 1.95-2.40 (5H, m), 3.93 (2H, t,  $J=6.4$  Hz), 4.05 (2H, d,  $J=7.8$  Hz), 4.97 (2H, s), 5.21 (2H, s), 6.98 (1H, d,  $J=2.6$  Hz), 7.16 (1H, dd,  $J=2.6, 8.8$  Hz), 7.28-7.45 (5H, m), 7.68-7.87 (4H, m),  
10 8.35 (1H, d,  $J=8.8$  Hz).

(7) To a solution of 2-[[6-benzyloxy-2-isobutyl-1-oxo-4-(4,4,4-trifluorobutoxy)-1,2-dihydro-3-isoquinolinyl]methyl]-1H-isoindole-1,3(2H)-dione (3.85 g, 6.5 mmol) in ethanol (30 mL) was added hydrazine  
15 monohydrate (0.95 mL, 19.5 mmol). The obtained mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over  
20 anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (30 mL) and di-*t*-butyl dicarbonate (2.2 mL, 9.8 mmol) was added thereto. The obtained mixture was stirred at room temperature for 1 h. The reaction  
25 mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to  
30 give *tert*-butyl [6-benzyloxy-2-isobutyl-1-oxo-4-(4,4,4-trifluorobutoxy)-1,2-dihydro-3-isoquinolinyl]-methylcarbamate (0.36 g, 87.8%) as crystals.

Melting point 117-118°C.

Elemental analysis for  $C_{32}H_{37}N_2O_5F_3$

35 Calculated: C, 64.04; H, 6.63; N, 4.98.

Found: C, 64.33; H, 6.75; N, 5.00.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.94 (6H, d, J=7.0 Hz), 1.46 (9H, s), 1.98-2.44 (5H, m), 3.78 (2H, t, J=6.2 Hz), 3.93 (2H, d, J=7.8 Hz), 4.46 (2H, d, J=5.2 Hz), 4.72 (1H, bs), 5.22 (2H, s), 6.97 (1H, d, J=2.4 Hz), 7.16 (1H, dd, J=2.4, 9.0 Hz), 7.31-7.46 (5H, m), 8.34 (1H, d, J=9.0 Hz).

(8) A suspension of tert-butyl [6-benzyloxy-2-isobutyl-1-oxo-4-(4,4,4-trifluorobutoxy)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (3.09 g, 5.5 mmol) and 5% palladium carbon (1.0 g) in tetrahydrofuran (20 mL) and ethanol (20 mL) was stirred under a hydrogen atmosphere at room temperature for 2 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [6-hydroxy-2-isobutyl-1-oxo-4-(4,4,4-trifluorobutoxy)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (2.48 g, 95.4%) as crystals.

Melting point 173-174°C.

Elemental analysis for C<sub>23</sub>H<sub>31</sub>N<sub>2</sub>O<sub>5</sub>F<sub>3</sub>

Calculated: C, 58.47; H, 6.61; N, 5.93.

Found: C, 58.61; H, 6.66; N, 5.84.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.95 (6H, d, J=7.0 Hz), 1.47 (9H, s), 2.03-2.45 (5H, m), 3.88 (2H, t, J=5.9 Hz), 3.98 (2H, d, J=7.4 Hz), 4.49 (2H, d, J=4.6 Hz), 4.77 (1H, bs), 7.08-7.14 (2H, m), 8.26 (1H, d, J=8.8 Hz), 8.86 (1H, bs).

(9) A solution of tert-butyl [6-hydroxy-2-isobutyl-4-(4,4,4-trifluorobutoxy)-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.47 g, 1 mmol), iodoacetamide (0.27 g, 1.5 mmol) and 1,8-diazabicyclo[5.4.0]-7-undecene (0.22 mL, 1.5 mmol) in N,N-dimethylformamide (10 mL) was stirred at 70°C for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give

tert-butyl [6-(2-amino-2-oxoethoxy)-2-isobutyl-4-(4,4,4-trifluorobutoxy)-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.25 g, 48.1%) as crystals.

5 Melting point 184-186°C.

Elemental analysis for  $C_{25}H_{34}N_3O_6F_3$

Calculated: C, 56.70; H, 6.47; N, 7.94.

Found: C, 56.43; H, 6.55; N, 7.87.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.96 (6H, d,  $J=6.6$  Hz), 1.47 (9H, s),  
10 2.05-2.23 (2H, m), 2.32-2.52 (2H, m), 3.91 (2H, t,  $J=6.4$  Hz), 3.96 (2H, d,  $J=7.6$  Hz), 4.49 (2H, d,  $J=5.9$  Hz), 4.62 (2H, s), 4.74 (1H, bs), 5.81 (1H, bs), 6.54 (1H, bs), 7.00 (1H, d,  $J=2.6$  Hz), 7.10 (1H, dd,  $J=2.6, 8.8$  Hz), 8.38 (1H, d,  $J=8.8$  Hz).

15 (10) To a solution of tert-butyl [6-(2-amino-2-oxoethoxy)-2-isobutyl-4-(4,4,4-trifluorobutoxy)-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.18 g, 0.35 mmol) in ethyl acetate (5 mL) was added a solution of 4N hydrogen chloride in ethyl acetate (5 mL) and the  
20 obtained solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol - diisopropyl ether to give  
25 2-[[[3-(aminomethyl)-2-isobutyl-1-oxo-4-(4,4,4-trifluorobutoxy)-1,2-dihydro-6-isoquinolinyl]oxy]acetamide hydrochloride (0.15 g, 93.8%) as crystals.

Melting point 147-148°C.

Elemental analysis for  $C_{20}H_{27}N_3O_4ClF_3 \cdot H_2O$

30 Calculated: C, 49.64; H, 6.04; N, 8.68.

Found: C, 49.73; H, 5.97; N, 8.60.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.88 (6H, d,  $J=6.6$  Hz), 1.96-2.13 (3H, m), 2.56-2.71 (2H, m), 3.93-4.02 (4H, m), 4.15 (2H, d,  $J=4.2$  Hz), 4.67 (2H, s), 7.05 (1H, d,  $J=2.4$  Hz), 7.24  
35 (1H, dd,  $J=2.4, 8.8$  Hz), 7.49 (1H, bs), 7.76 (1H, bs), 8.20 (1H, d,  $J=8.8$  Hz), 8.73 (3H, s).

**Example 165**

2-[[3-(Aminomethyl)-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyloxy]acetamide hydrochloride

- (1) A mixed solution of methyl 6-benzyloxy-2-isobutyl-1-oxo-4-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinecarboxylate (7.70 g, 15 mmol), 4-fluorophenylboronic acid (2.52 g, 18 mmol) and sodium carbonate (3.97 g, 37.5 mmol) in toluene (50 mL), methanol (10 mL) and water (10 mL) was stirred under an argon atmosphere at room temperature for 30 min. To the obtained mixture was added tetrakis(triphenylphosphine)palladium (0.87 g, 0.9 mmol) and the mixture was refluxed under heating under an argon atmosphere for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give methyl 6-benzyloxy-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (5.16 g, 74.9%) as crystals.

Melting point 118-119°C.

Elemental analysis for  $C_{28}H_{26}NO_4F$

- Calculated: C, 73.19; H, 5.70; N, 3.05.

Found: C, 72.92; H, 5.79; N, 2.97.

- $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.92 (6H, d,  $J=6.6$  Hz), 2.02-2.21 (1H, m), 3.49 (3H, s), 3.93 (2H, d,  $J=7.8$  Hz), 4.99 (2H, s), 6.54 (1H, d,  $J=2.4$  Hz), 7.07-7.40 (10H, m), 8.43 (1H, d,  $J=8.8$  Hz).

- (2) To a solution of methyl 6-benzyloxy-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (5.05 g, 11 mmol) in methanol (30 mL) was added an aqueous solution (10 mL) of lithium hydroxide monohydrate (1.38 g, 33 mmol). The obtained mixture was refluxed under heating for 12 h. The



reaction mixture was poured into water, and, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under  
5 reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give 6-benzyloxy-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (3.94 g, 80.5%) as crystals.

10 Melting point 236-237°C.

Elemental analysis for  $C_{27}H_{24}NO_4F$

Calculated: C, 72.80; H, 5.43; N, 3.14.

Found: C, 72.41; H, 5.28; N, 3.02.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.86 (6H, d,  $J=6.6$  Hz), 2.10-2.24 (1H, m), 3.89 (2H, d,  $J=7.4$  Hz), 4.99 (2H, s), 6.52 (1H, d,  $J=2.2$  Hz), 7.04-7.16 (3H, m), 7.24-7.37 (7H, m), 8.25 (1H, d,  $J=9.2$  Hz).

(3) To a solution of 6-benzyloxy-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid  
20 (3.79 g, 8.5 mmol) in tetrahydrofuran (30 mL) were added oxalyl chloride (0.9 mL, 10.2 mmol) and N,N-dimethylformamide (3 drops), and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was  
25 dissolved in tetrahydrofuran (20 mL). The obtained solution was added dropwise to a suspension of sodium tetrahydroborate (1.13 g, 30 mmol) in 1,2-dimethoxyethane (30 mL) at 0°C. The obtained mixture was stirred at 0°C for 1 h. The reaction mixture was poured  
30 into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 6-benzyloxy-4-(4-fluorophenyl)-3-hydroxymethyl-2-isobutyl-1(2H)-  
35 isoquinolinone (3.31 g, 90.2%) as crystals.

Melting point 143-144°C.

Elemental analysis for  $C_{27}H_{26}NO_3F$

Calculated: C, 75.15; H, 6.07; N, 3.25.

Found: C, 75.04; H, 6.28; N, 3.22.

5  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.94 (6H, d,  $J=6.6$  Hz), 2.11-2.25 (1H, m), 2.70 (1H, bs), 4.16 (2H, d,  $J=7.8$  Hz), 4.41 (2H, d,  $J=5.4$  Hz), 4.89 (2H, s), 6.28 (1H, d,  $J=2.4$  Hz), 6.93-6.98 (1H, m), 7.13-7.34 (9H, m), 8.20-8.26 (1H, m).

(4) To a suspension of 6-benzyloxy-4-(4-fluorophenyl)-3-hydroxymethyl-2-isobutyl-1(2H)-isoquinolinone (3.24 g, 7.5 mmol) in toluene (50 mL) was added thionyl chloride (1.1 mL, 15 mmol). The obtained mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 6-benzyloxy-3-chloromethyl-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone (3.18 g, 94.4%) as crystals.

20  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (6H, d,  $J=7.0$  Hz), 2.13-2.31 (1H, m), 4.14 (2H, d,  $J=7.6$  Hz), 4.35 (2H, s), 4.95 (2H, s), 6.35 (1H, d,  $J=2.6$  Hz), 7.11-7.38 (10H, m), 8.41 (1H, d,  $J=8.8$  Hz).

25 (5) A solution of 6-benzyloxy-3-chloromethyl-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone (3.15 g, 7 mmol) and potassium phthalimide (1.94 g, 10.5 mmol) in *N,N*-dimethylformamide (100 mL) was stirred at room temperature for 6 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was crystallized from ethyl acetate - diisopropyl ether to give 2-[[6-benzyloxy-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methyl]-1H-isoindole-1,3(2H)-

dione (3.42 g, 87.2%) as crystals.

Melting point 198-199°C.

Elemental analysis for  $C_{35}H_{29}N_2O_4F$

Calculated: C, 74.98; H, 5.21; N, 5.00.

5 Found: C, 74.83; H, 5.01; N, 4.82.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.98 (6H, d,  $J=6.6$  Hz), 2.13-2.27 (1H, m), 4.02 (2H, d,  $J=7.4$  Hz), 4.94 (2H, s), 6.31 (1H, d,  $J=2.6$  Hz), 7.02-7.14 (3H, m), 7.20-7.38 (7H, m), 7.66-7.78 (4H, m), 8.39 (1H, d,  $J=9.2$  Hz).

10 (6) To a solution of 2-[[6-benzyloxy-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methyl]-1H-isoindole-1,3(2H)-dione (3.36 g, 6 mmol) in ethanol (30 mL) was added hydrazine monohydrate (0.9 mL, 18 mmol).

The obtained mixture was refluxed under heating for 2 h.

15 The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in

20 tetrahydrofuran (20 mL) and di-*t*-butyl dicarbonate (2.1 mL, 9 mmol) was added thereto. The obtained mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over

25 anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give *tert*-butyl [6-benzyloxy-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-

30 isoquinolinyl]methylcarbamate (3.16 g, 99.4%) as crystals.

Melting point 184-185°C.

Elemental analysis for  $C_{32}H_{35}N_2O_4F$

Calculated: C, 72.43; H, 6.65; N, 5.28.

35 Found: C, 72.07; H, 6.52; N, 5.18.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.98 (6H, d,  $J=6.6$  Hz), 1.42 (9H, s),

2.14-2.27 (1H, m), 4.02 (2H, d, J=6.9 Hz), 4.15 (2H, d, J=5.4 Hz), 4.52 (1H, bs), 4.94 (2H, s), 6.29 (1H, d, J=2.4 Hz), 7.06-7.11 (1H, m), 7.16-7.36 (9H, m), 8.34-8.38 (1H, m).

- 5 (7) A suspension of tert-butyl [6-benzyloxy-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (2.65 g, 5 mmol) and 5% palladium carbon (0.8 g) in ethanol (20 mL) and tetrahydrofuran (20 mL) was stirred under a hydrogen  
10 atmosphere at room temperature for 2 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran - diisopropyl ether to give tert-butyl [4-(4-fluorophenyl)-6-hydroxy-2-  
15 isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (3.11 g, 94.2%) as crystals.

Melting point 229-230°C.

Elemental analysis for  $C_{25}H_{29}N_2O_4F$

- 20 Calculated: C, 68.16; H, 6.64; N, 6.36.

Found: C, 67.98; H, 6.88; N, 6.20.

- $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.95 (6H, d, J=6.6 Hz), 1.42 (9H, s),  
2.11-2.24 (1H, m), 4.00 (1H, d, J=7.4 Hz), 4.16 (2H, d, J=3.6 Hz), 4.49 (1H, bs), 6.33 (1H, d, J=2.4 Hz), 7.03  
25 (1H, dd, J=2.4, 9.0 Hz), 7.06-7.18 (4H, m), 7.90 (1H, bs), 8.26 (1H, d, J=9.0 Hz).

- (8) A solution of tert-butyl [4-(4-fluorophenyl)-6-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.44 g, 1 mmol), 2-  
30 iodoacetamide (0.37 g, 2 mmol) and 1,8-diazabicyclo[5.4.0]-7-undecene (0.30 mL, 2 mmol) in N,N-dimethylformamide (10 mL) was stirred at 80°C for 10 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine,  
35 dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by

silica gel column chromatography to give tert-butyl [6-(2-amino-2-oxoethoxy)-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.24 g, 49.0%) as crystals.

<sup>5</sup> Melting point 218-219°C.

Elemental analysis for C<sub>27</sub>H<sub>32</sub>N<sub>3</sub>O<sub>5</sub>F

Calculated: C, 65.18; H, 6.48; N, 8.45.

Found: C, 64.84; H, 6.75; N, 8.25.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.99 (6H, d, J=7.0 Hz), 1.43 (9H, s),  
<sup>10</sup> 2.13-2.30 (1H, m), 4.04 (2H, d, J=7.6 Hz), 4.17 (2H, d, J=5.6 Hz), 4.35 (2H, s), 4.54 (1H, bs), 5.75 (1H, bs), 6.28 (1H, d, J=2.5 Hz), 6.49 (1H, bs), 7.04 (1H, dd, J=2.5, 9.0 Hz), 7.21-7.24 (4H, m), 8.42 (1H, d, J=9.0 Hz).

<sup>15</sup> (9) To a solution of tert-butyl [6-(2-amino-2-oxoethoxy)-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.20 g, 0.4 mmol) in ethyl acetate (5 mL) was added a solution of 4N hydrogen chloride in ethyl acetate (5 mL) and the  
<sup>20</sup> obtained solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate - diisopropyl ether to give 2-[[3-(aminomethyl)-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-  
<sup>25</sup> isoquinolinyl]oxy]acetamide hydrochloride (0.16 g, 94.1%) as crystals.

Melting point 189-190°C.

Elemental analysis for C<sub>22</sub>H<sub>25</sub>N<sub>3</sub>O<sub>3</sub>FCl

Calculated: C, 65.18; H, 6.48; N, 8.45.

<sup>30</sup> Found: C, 64.84; H, 6.75; N, 8.25.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.91 (6H, d, J=6.6 Hz), 1.99-2.18 (1H, m), 3.84 (2H, bs), 4.04 (2H, d, J=6.6 Hz), 4.38 (2H, s), 6.29 (1H, d, J=2.0 Hz), 7.20 (1H, dd, J=2.0, 9.0 Hz), 7.34 (1H, bs), 7.38-7.43 (4H, m), 7.56 (1H, bs), 8.27  
<sup>35</sup> (1H, d, J=9.0 Hz), 8.53 (3H, bs).

Example 166

3-(Aminomethyl)-2-isobutyl-6-(5-methyl-1,3,4-oxadiazol-3-yl)-4-phenyl-1(2H)-isoquinolinone

(1) A mixture of methyl 3-[(tert-butoxycarbonyl)amino]methyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxylate (0.24 g, 0.53 mmol), hydrazine monohydrate (0.65 mL, 13.3 mmol) and methanol (6 mL) was stirred in a sealed tube at 75°C. The reaction mixture was concentrated under reduced pressure and to the residue was added methanol - water (1:1, 4 mL) to allow precipitation of a solid. This solid was collected by filtration, washed with water and dried in vacuo to give tert-butyl [6-(hydrazinocarbonyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.23 g, 94%) as a colorless solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.00 (6H, d, J=7.0 Hz), 1.43 (9H, s), 2.15-2.35 (1H, m), 4.08 (2H, d, J=7.0 Hz), 4.20 (2H, d, J=5.2 Hz), 4.70 (1H, br), 7.20-7.30 (3H, m), 7.45-7.55 (3H, m), 7.69 (1H, d, J=5.4 Hz), 8.43 (1H, d, J=8.6 Hz).

(2) A mixture of tert-butyl [6-(hydrazinocarbonyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.23 g, 0.50 mmol), triethyl orthoacetate (2.0 mL, 10.9 mmol) and n-butanol (10 mL) was refluxed under heating for 20 min. To the reaction mixture was added 1,8-diazabicyclo[5.4.0]-7-undecene (0.075 mL, 0.50 mmol) and the mixture was refluxed under heating for 1 h. To this reaction mixture was added acetic acid (0.040 mL, 0.70 mmol) and the mixture was concentrated under reduced pressure.

The residue was partitioned between water (10 mL) and ethyl acetate (30 mL), and the organic layer was washed with water (20 mL), dried over anhydrous magnesium sulfate (9 g) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate=2:1 (v/v)) to give tert-butyl [2-isobutyl-6-(5-methyl-1,3,4-oxadiazol-

3-yl)-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.22 g, 91%) as a colorless powder.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.02 (6H, d, J=7.2 Hz), 1.43 (9H, s),  
5 2.15-2.35 (1H, m), 2.57 (3H, s), 4.10 (2H, d, J=7.2 Hz),  
4.22 (2H, d, J=5.4 Hz), 4.57 (1H, br), 7.20-7.35 (2H, m),  
7.50-7.65 (4H, m), 8.05 (1H, dm, J=8.4 Hz), 8.58 (1H, dd,  
J=2.8, 8.4 Hz).

(3) To tert-butyl [2-isobutyl-6-(5-methyl-1,3,4-oxadiazol-3-yl)-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.20 g, 0.41 mmol) was added a solution (4 mL) of 4N hydrogen chloride in ethyl acetate and the mixture was stirred at room temperature for 17 h. The reaction mixture was concentrated under  
15 reduced pressure and to the residue was added diisopropyl ether (5 mL). The precipitated powder was collected by filtration. To this powder was added saturated aqueous sodium hydrogencarbonate (30 mL) and the mixture was extracted twice with a solution (25 mL)  
20 of ethyl acetate - tetrahydrofuran (1:1). The organic layers were combined and the mixture was washed with saturated brine (25 mL), dried over anhydrous magnesium sulfate (15 g) and concentrated under reduced pressure. The residue was purified by silica gel column  
25 chromatography (ethyl acetate:methanol=20:1 (v/v)) and recrystallized from n-hexane - ethyl acetate (5:1) to give the title compound (0.11 g, 72%) as pale-yellow crystals.

Elemental analysis for C<sub>23</sub>H<sub>24</sub>N<sub>4</sub>O<sub>2</sub>,

30 Calculated: C, 71.11; H, 6.23; N, 14.42.

Found: C, 71.09; H, 6.28; N, 14.37.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.02 (6H, d, J=6.6 Hz), 2.15-2.40 (1H, m), 2.57 (3H, s), 3.69 (2H, bs), 4.24 (2H, d, J=7.4 Hz),  
7.25-7.35 (2H, m), 7.45-7.60 (2H, m), 7.62 (1H, d, J=1.0  
35 Hz), 8.05 (1H, dd, J=1.6, 8.4 Hz), 8.59 (1H, d, J=8.4 Hz).

Melting point 179-181°C

**Example 167**

6-Acetyl-3-(aminomethyl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone hydrochloride

- 5 (1) To a mixture of 3-[[tert-butoxycarbonyl]amino]methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxylic acid (0.81 g, 1.8 mmol), N,O-dimethylhydroxylamine hydrochloride (0.211 g, 2.16 mmol), 1-hydroxy-1H-benzotriazole monohydrate
- 10 (0.365 g, 2.7 mmol), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (0.517 g, 2.7 mmol) and N,N-dimethylformamide (10 mL) was added triethylamine (0.301 mL, 2.16 mmol), and the mixture was stirred at room temperature for 17 h. The reaction mixture was poured
- 15 into 0.1 M aqueous citric acid solution (100 mL) and extracted 3 times with ethyl acetate (50 mL). The organic layers were combined, washed once with 0.1 M aqueous citric acid solution (50 mL), twice with
- 20 saturated aqueous sodium hydrogencarbonate (50 mL) and once with saturated brine (50 mL), dried over anhydrous magnesium sulfate (15 g), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate=3:4 (v/v)) to give tert-butyl (2-isobutyl-6-
- 25 {[methoxy(methyl)amino]carbonyl}-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.83 g, 94%) as a colorless solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.02 (6H, d, J=7.0 Hz), 1.43 (9H, s), 2.15-2.35 (1H, m), 3.27 (3H, s), 3.42 (3H, s), 4.09 (2H, d, J=7.2 Hz), 4.21 (2H, d, J=5.4 Hz), 4.43 (1H, br), 7.20-7.30 (3H, m), 7.45-7.55 (3H, m), 7.69 (1H, dd, J=1.6, 8.2 Hz), 8.50 (1H, d, J=8.2 Hz).

- (2) Tert-butyl (2-isobutyl-6-  
35 {[methoxy(methyl)amino]carbonyl}-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.175 g, 0.355 mmol) was dissolved in tetrahydrofuran (5 mL) and a



solution (0.15 mL, 0.43 mmol) of 3 M methyl magnesium bromide in diethyl ether was added dropwise under ice-cooling. This mixture was stirred at room temperature for 1 h and quenched with saturated aqueous ammonium chloride solution (5 mL). The whole was extracted with ethyl acetate (10 mL), and the organic layer was washed once each with 0.1 M aqueous citric acid solution (10 mL), saturated aqueous sodium hydrogencarbonate (10 mL) and saturated brine (10 mL), dried over anhydrous magnesium sulfate (12 g) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate=5:2 (v/v)) to give tert-butyl (6-acetyl-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.132 g, 83%) as a colorless powder.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 1.01 (6H, d,  $J=7.2$  Hz), 1.43 (9H, s), 2.15-2.35 (1H, m), 2.27 (3H, s), 4.10 (2H, d,  $J=7.2$  Hz), 4.23 (2H, d,  $J=5.4$  Hz), 4.49 (1H, br), 7.20-7.30 (2H, m), 7.45-7.65 (4H, m), 7.96 (1H, dd,  $J=1.8, 8.4$  Hz), 8.54 (1H, d,  $J=8.4$  Hz).

(3) Tert-butyl (6-acetyl-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.10 g, 0.22 mmol) was dissolved in ethyl acetate (4 mL) and a solution (1 mL) of 4N hydrogen chloride in ethyl acetate was added thereto. The mixture was stirred at room temperature for 17 h. The reaction mixture was concentrated under reduced pressure and the residue was precipitated from ethyl acetate - diisopropyl ether (1:10) to give the title compound (0.084 g, 98%) as a pale-yellow powder.

Elemental analysis for  $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_2 \cdot \text{HCl} \cdot \text{H}_2\text{O}$ ,

Calculated: C, 65.58; H, 6.75; N, 6.95.

Found: C, 66.25; H, 6.73; N, 6.83.

$^1\text{H-NMR}(\text{CD}_3\text{OD})$   $\delta$ : 1.02 (6H, d,  $J=6.6$  Hz), 2.10-2.30 (1H, m), 2.50 (3H, s), 4.05-4.20 (4H, m), 7.35-7.45 (2H, m), 7.55-7.70 (4H, m), 8.15 (1H, dd,  $J=1.4, 8.4$  Hz), 8.53

(1H, d, J=8.4 Hz).

Melting point 179°C (decomposition)

**Example 168**

3-(Aminomethyl)-2-isobutyl-6-(1,3-oxazol-5-yl)-4-phenyl-

5 1(2H)-isoquinolinone hydrochloride

(1) Tert-Butyl (6-formyl-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.20 g, 0.45 mmol) was dissolved in methanol (10 mL) and p-toluene sulfonylmethylisocyanide (0.088 g, 0.45 mmol) and

10 potassium carbonate (0.125 g, 0.90 mmol) were added.

This mixture was refluxed under heating for 30 min and the reaction mixture was partitioned between saturated aqueous sodium hydrogencarbonate (50 mL) and ethyl acetate - tetrahydrofuran (1:1 (v/v), 50 mL). The

15 organic layer was washed once each with saturated aqueous sodium hydrogencarbonate (50 mL) and saturated brine (50 mL), dried over anhydrous magnesium sulfate (12 g) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography  
20 (n-hexane:ethyl acetate=2:1 (v/v)) to give tert-butyl [2-isobutyl-6-(1,3-oxazol-5-yl)-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.16 g, 75%) as a colorless solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.02 (6H, d, J=7.0 Hz), 1.43 (9H, s),  
25 2.15-2.40 (1H, m), 4.09 (2H, d, J=7.2 Hz), 4.22 (2H, d, J=5.6 Hz), 4.51 (1H, br), 7.20 (1H, d, J=1.4 Hz), 7.20-7.35 (2H, m), 7.31 (1H, s), 7.45-7.60 (3H, m), 7.70 (1H, dd, J=1.4, 8.4 Hz), 7.86 (1H, s), 8.51 (1H, d, J=8.4 Hz).

(2) Tert-butyl [2-isobutyl-6-(1,3-oxazol-5-yl)-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.14  
30 g, 0.30 mmol) was dissolved in methanol (4 mL) and a solution (10 mL) of 4N hydrogen chloride in ethyl acetate were added thereto. This mixture was stirred at room temperature for 1 h and the precipitated crystals  
35 were collected by filtration to give the title compound (0.084 g, 69%) as a colorless powder.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.93 (6H, d, J=6.6 Hz), 2.10-2.20 (1H, m), 3.80-4.10 (4H, m), 7.16 (1H, d, J=1.6 Hz), 7.40-7.50 (2H, m), 7.55-7.65 (3H, m), 7.95-8.00 (1H, m), 8.30 (3H, br), 8.40 (1H, d, J=8.8 Hz), 8.43 (1H, s).

5 Melting point 217°C (decomposition)

**Example 169**

3-(Aminomethyl)-2-isobutyl-4-phenyl-6-(2H-tetrazol-5-yl)-1(2H)-isoquinolinone hydrochloride

(1) To a solution (30 mL) of tert-butyl (6-cyano-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.86 g, 2.0 mmol) in toluene were added sodium azide (0.16 g, 2.5 mmol) and triethylamine hydrochloride (0.28 g, 2.5 mmol), and the mixture was stirred at 90°C for 24 h. The reaction mixture was poured into water (100 mL), acidified with 1N hydrochloric acid and extracted twice with ethyl acetate (50 mL). The extracts were combined and washed with saturated brine (15 mL), dried over anhydrous magnesium sulfate (12 g) and concentrated under reduced pressure. The residue was recrystallized from tetrahydrofuran - diisopropyl ether (1:5) to give tert-butyl [2-isobutyl-1-oxo-4-phenyl-6-(2H-tetrazol-5-yl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.36 g, 37%) as colorless crystals.

25 <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.00 (6H, d, J=6.6 Hz), 1.45 (9H, s), 2.15-2.35 (1H, m), 4.15 (2H, bd, J=7.4 Hz), 4.22 (2H, bd, J=5.0 Hz), 7.25-7.50 (6H, m), 7.73 (1H, bs), 8.05 (1H, dm, J=8.4 Hz), 8.44 (1H, d, J=8.4 Hz).

(2) Tert-butyl [2-isobutyl-1-oxo-4-phenyl-6-(2H-tetrazol-5-yl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.15 g, 0.32 mmol) was dissolved in tetrahydrofuran (4 mL) and a solution (4 mL) of 4N hydrogen chloride in ethyl acetate was added thereto. This mixture was stirred at room temperature for 17 h, and the precipitated crystals were collected by filtration to give the title compound (0.13 g, 97%)

as colorless crystals.

Elemental analysis for  $C_{21}H_{22}N_6O \cdot HCl \cdot 0.5H_2O$

Calculated: C, 57.60; H, 5.98; N, 19.19.

Found: C, 57.41; H, 5.96; N, 18.73.

<sup>1</sup>H-NMR(DMSO- $d_6$ )  $\delta$ : 0.94 (6H, d, J=6.6 Hz), 2.10-2.20 (1H, m), 3.90 (2H, bs), 4.10 (2H, d, J=6.6 Hz), 7.40-7.50 (2H, m), 7.55-7.65 (3H, m), 7.69 (1H, d, J=1.5 Hz), 8.23 (1H, dd, J=1.5, 8.1 Hz), 8.52 (3H, br), 8.54 (1H, d, J=8.1 Hz).

10 Melting point 218-220°C

**Example 170**

3-(Aminomethyl)-2-isobutyl-6-(methylsulfanyl)-4-phenyl-1(2H)-isoquinolinone hydrochloride

- (1) A mixture of 3-(aminomethyl)-6-bromo-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (0.19 g, 0.50 mmol), sodium thiomethoxide (0.043 g, 0.60 mmol) and dimethylsulfide (2 mL) was stirred at 70°C for 2 h. To the reaction mixture was added another sodium thiomethoxide (0.043 g, 0.60 mmol), and the resulting mixture was stirred at 70°C for 2 h. The reaction mixture was partitioned between water (100 mL) and ethyl acetate (25 mL) and the aqueous layer was extracted with ethyl acetate (25 mL). The extracts were combined and washed once each with saturated aqueous sodium hydrogencarbonate (25 mL) and saturated brine (25 mL), dried over anhydrous magnesium sulfate (12 g) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate=1:5 (v/v)) to give 3-(aminomethyl)-2-isobutyl-6-(methylsulfanyl)-4-phenyl-1(2H)-isoquinolinone (0.16 g, 88%) as an oil.
- <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$ : 1.00 (6H, d, J=6.6 Hz), 2.15-2.35 (1H, m), 2.32 (3H, s), 3.66 (2H, bs), 4.19 (2H, d, J=7.8 Hz), 6.69 (1H, d, J=1.8 Hz), 7.20-7.30 (3H, m), 7.45-7.55 (3H, m), 8.36 (1H, d, J=8.4 Hz).
- (2) 3-(Aminomethyl)-2-isobutyl-6-(methylsulfanyl)-4-phenyl-1(2H)-isoquinolinone (0.13 g, 0.37 mmol) was

dissolved in ethyl acetate (3 mL) and a solution (1 mL) of 4N hydrogen chloride in ethyl acetate was added thereto. The mixture was stirred for 5 min and concentrated under reduced pressure. The obtained

5 residue was crystallized from ethyl acetate - diisopropyl ether (1:2) to give the title compound (0.14 g, 95%) as colorless crystals.

Elemental analysis for  $C_{21}H_{24}N_2OS \cdot HCl$ ,  
Calculated: C, 64.85; H, 6.48; N, 7.20.

10 Found: C, 64.79; H, 6.55; N, 6.99.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.91 (6H, d,  $J=6.6$  Hz), 1.95-2.20 (1H, m), 2.34 (3H, s), 3.86 (2H, bs), 4.00-4.15 (2H, m), 6.59 (1H, d,  $J=1.8$  Hz), 7.35-7.65 (6H, m), 8.23 (1H, d,  $J=8.4$  Hz), 8.46 (1H, bs), 8.58 (2H, bs).

15 Melting point 252-255°C

#### Example 171

2-[[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]sulfanyl]acetamide

A solution (2 mL) of 2-mercaptoacetamide (0.27 g, 20 3.0 mmol) in N,N-dimethylformamide was ice-cooled under a nitrogen atmosphere and sodium hydride (0.12 g, 3.0 mmol) (60% in oil) was added thereto. The resulting mixture was stirred under ice-cooling for 30 min. To the obtained suspension was added 3-(aminomethyl)-6-25 bromo-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (1.06 g, 2.74 mmol), and the mixture was stirred at 80°C for 24 h. The reaction mixture was partitioned between water (100 mL) and ethyl acetate (50 mL), and the aqueous layer was extracted twice with ethyl acetate (50 mL). The 30 extracts were combined and washed with saturated brine (20 mL), dried over anhydrous magnesium sulfate (12 g) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:methanol=1:0-10:1 (v/v)) and recrystallized from 35 n-hexane - ethyl acetate (1:1) to give the title compound (0.54 g, 50%) as a colorless powder.

Elemental analysis for  $C_{22}H_{25}N_3O_2S$ ,

Calculated: C, 66.81; H, 6.37; N, 10.62.

Found: C, 66.40; H, 6.41; N, 10.26.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (6H, d,  $J=6.6$  Hz), 2.20-2.30 (1H, m), 3.52 (2H, s), 3.66 (2H, bs), 4.19 (2H, d,  $J=7.4$  Hz), 5.39 (1H, bs), 6.41 (1H, bs), 6.79 (1H, d,  $J=1.8$  Hz), 7.20-7.35 (3H, m), 7.45-7.55 (3H, m), 8.36 (1H, d,  $J=8.6$  Hz).

Melting point 218-220°C

10 **Example 172**

3-(Aminomethyl)-2-isobutyl-6-(methylsulfinyl)-4-phenyl-1(2H)-isoquinolinone

To a mixture of 3-(aminomethyl)-2-isobutyl-6-(methylsulfinyl)-4-phenyl-1(2H)-isoquinolinone (0.18 g; 0.52 mmol), conc. sulfuric acid (0.0168 mL, 0.31 mmol), methanol (2 mL) and water (5 mL) was added Oxone® (0.19 g, 0.31 mmol), and the mixture was stirred at room temperature for 30 min. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate (50 mL) and extracted 3 times with ethyl acetate (25 mL). The extracts were combined, washed with saturated brine (10 mL), dried over anhydrous magnesium sulfate (9 g) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:methanol=10:1 (v/v)). The resulting oil was solidified from diisopropyl ether (1 mL) to give the title compound (0.081 g, 42%) as a pale-yellow powder.

Elemental analysis for  $C_{21}H_{24}N_2O_2S \cdot 2H_2O$ ,

Calculated: C, 62.35; H, 6.98; N, 6.93.

30 Found: C, 62.27; H, 6.58; N, 6.36.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.01 (6H, d,  $J=6.6$  Hz), 2.20-2.35 (1H, m), 2.66 (3H, s), 3.69 (2H, bs), 4.24 (2H, d,  $J=7.4$  Hz), 7.20-7.35 (3H, m), 7.45-7.55 (3H, m), 7.64 (1H, dd,  $J=1.8, 8.6$  Hz), 8.63 (1H, d,  $J=8.6$  Hz).

35 Melting point 167°C (decomposition)

**Example 173**

3-(Aminomethyl)-2-isobutyl-6-(methylsulfonyl)-4-phenyl-1(2H)-isoquinolinone hydrochloride

(1) A mixture of tert-butyl (6-bromo-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.24 g, 0.5 mmol), sodium thiomethoxide (0.080 g, 1.1 mmol) and N,N-dimethylformamide (4 mL) was stirred at 85°C for 1 h, and the reaction mixture was poured into water (50 mL) and extracted twice with ethyl acetate (25 mL). The extracts were combined, washed with saturated aqueous sodium hydrogencarbonate (15 mL) and saturated brine (15 mL), dried over anhydrous magnesium sulfate (12 g) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate=4:1 (v/v)) to give tert-butyl [2-isobutyl-6-(methylsulfonyl)-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.17 g, 73%) as a colorless powder.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.00 (6H, d, J=6.6 Hz), 1.43 (9H, s), 2.15-2.35 (1H, m), 2.32 (3H, s), 4.06 (2H, d, J=7.8 Hz), 4.19 (2H, d, J=6.0 Hz), 4.46 (1H, br), 6.68 (1H, d, J=1.8 Hz), 7.20-7.35 (3H, m), 7.40-7.60 (3H, m), 8.34 (1H, d, J=8.4 Hz).

(2) To a solution (5 mL) of tert-butyl [2-isobutyl-6-(methylsulfonyl)-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.17 g, 0.37 mmol) in dichloromethane was added m-chloroperbenzoic acid (0.13 g, 0.77 mmol) under ice-cooling, and the mixture was stirred at room temperature for 1 h. The reaction mixture was washed once with 5% aqueous sodium thiosulfate solution (15 mL) and twice with saturated aqueous sodium hydrogencarbonate (15 mL), and partitioned using a PTFE tube. The organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate=2:1 (v/v)) to give tert-butyl [2-isobutyl-6-(methylsulfonyl)-1-oxo-4-phenyl-1,2-dihydro-

3-isoquinolinyl]methylcarbamate (0.16 g, 93%) as a colorless oil.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.01 (6H, d, J=6.6 Hz), 1.43 (9H, s), 2.15-2.35 (1H, m), 2.99 (3H, s), 4.12 (2H, d, J=6.9 Hz), 4.24 (2H, d, J=6.0 Hz), 4.42 (1H, br), 7.30-7.35 (2H, m), 7.50-7.60 (4H, m), 7.94 (1H, dd, J=1.8, 8.4 Hz), 8.66 (1H, d, J=8.4 Hz).

(3) A mixture of tert-butyl [2-isobutyl-6-(methylsulfonyl)-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.16 g, 0.33 mmol) and a solution (5 mL) of 4N hydrogen chloride in ethyl acetate was stirred for 1 h and concentrated under reduced pressure. The obtained residue was precipitated from ethyl acetate - diisopropyl ether (1:10) to give the title compound (0.12 g, 87%) as a colorless powder.

Elemental analysis for C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub>S HCl H<sub>2</sub>O 0.25IPE, Calculated: C, 58.18; H, 6.62; N, 6.03.

Found: C, 58.15; H, 6.87; N, 5.89.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.93 (6H, d, J=6.6 Hz), 2.05-2.20 (1H, m), 3.22 (3H, s), 3.90 (2H, bs), 4.11 (2H, bd, J=6.6 Hz), 7.40-7.50 (3H, m), 7.55-7.70 (3H, m), 8.09 (1H, dd, J=1.8, 8.4 Hz), 8.57 (1H, d, J=8.4 Hz), 8.60 (1H, br). Melting point 209°C (decomposition)

#### Example 174

3-(Aminomethyl)-2-isobutyl-6-(methanesulfonylamino)-4-phenyl-1(2H)-isoquinolinone hydrochloride

This compound was synthesized according to the method similar to that in Example 88 from 6-amino-3-(tert-butoxycarbonylaminoethyl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 111 (1)).

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.91 (6H, d, J=6.6 Hz), 2.08 (1H, m), 2.98 (3H, s), 3.85 (2H, s), 4.03 (2H, d, J=6.2 Hz), 6.75 (1H, d, J=1.8 Hz), 7.36-7.44 (3H, m), 7.54-7.58 (3H, m), 7.77 (1H, d, J=8.8 Hz), 8.46 (3H, bs), 10.29 (1H, bs).

#### Example 175



3-(Aminomethyl)-2-isobutyl-6-(methoxycarbonylamino)-4-phenyl-1(2H)-isoquinolinone hydrochloride

This compound was synthesized according to the method similar to that in Example 88 from 6-amino-3-(tert-butoxycarbonylaminomethyl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 111 (1)).

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.91 (6H, d, J=6.6 Hz), 2.08 (1H, m), 3.59 (3H, s), 3.85 (2H, s), 4.02 (2H, d, J=6.6Hz), 7.22 (1H, d, J=1.8Hz), 7.34-7.38 (2H, m), 7.54-7.63 (5H, m), 8.23 (1H, d, J=8.8Hz), 8.40 (3H, bs), 10.04 (1H, s).

Example 176

3-(Aminomethyl)-2-isobutyl-6-(dimethanesulfonylamino)-4-phenyl-1(2H)-isoquinolinone hydrochloride

This compound was synthesized according to the method similar to that in Example 88 from 6-amino-3-(tert-butoxycarbonylaminomethyl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (synthesized according to the method similar to that in Example 111 (1)).

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.93 (6H, d, J=6.6 Hz), 2.11 (1H, m), 3.34 (3H, s), 3.44 (2H, s), 3.90 (2H, s), 4.08 (2H, d, J=7.4Hz), 6.86 (1H, d, J=1.8Hz), 7.41-7.45 (2H, m), 7.57-7.60 (3H, m), 7.73 (1H, dd, J=8.4, 1.8Hz), 8.43 (1H, d, J=8.4Hz), 8.44 (3H, bs).

Example 177

N-{3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl}-N'-methylurea hydrochloride

This compound was synthesized according to the method similar to that in Example 80 from 3-(tert-butoxycarbonylaminomethyl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxylic acid (synthesized according to the method similar to that in Example 108 (1)).

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.90 (6H, d, J=6.6 Hz), 2.07 (1H, m), 2.56 (3H, s), 3.81 (2H, s), 4.00 (2H, d, J=7.0Hz), 6.17 (1H, bs), 6.98 (1H, d, J=2.0Hz), 7.34-7.38 (2H, m), 7.54-7.67 (4H, m), 8.17 (1H, d, J=8.8Hz), 8.39 (3H, bs),

9.13 (1H, s).

**Example 178**

N-{3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl}-N',N'-dimethylurea

5 hydrochloride

This compound was synthesized according to the method similar to that in Example 80 from 3-(tert-butoxycarbonylaminomethyl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxylic acid (synthesized according to the method similar to that in Example 108 (1)).

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.91 (6H, d, J=6.6 Hz), 2.07 (1H, m), 2.86 (6H, s), 3.81 (2H, s), 4.02 (2H, d, J=7.0Hz), 7.13 (1H, s), 7.34-7.38 (2H, m), 7.54-7.57 (3H, m), 7.69 (1H, d, J=8.8Hz), 8.17 (1H, d, J=8.8Hz), 8.41 (3H, bs), 8.68 (1H, s).

**Example 179**

N-{3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl}urea hydrochloride

This compound was synthesized according to the method similar to that in Example 80 from 3-(tert-butoxycarbonylaminomethyl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone-6-carboxylic acid (synthesized according to the method similar to that in Example 108 (1)).

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.91 (6H, d, J=6.6 Hz), 2.07 (1H, m), 3.82 (2H, d, J=4.0Hz), 4.02 (2H, d, J=7.2Hz), 5.96 (1H, bs), 6.70 (1H, bs), 6.51 (1H, d, J=1.8Hz), 7.35-7.39 (2H, m), 7.51-7.59 (3H, m), 7.79 (1H, dd, J=8.8, 1.8Hz), 8.18 (1H, d, J=8.8Hz), 8.44 (3H, bs), 9.10 (1H, s).

**Example 180**

30 (E)-3-[3-(Aminomethyl)-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide hydrochloride

(1) To a solution of tert-butyl [4-(4-fluorophenyl)-6-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (2.00 g, 3.5 mmol) in N,N-dimethylformamide (30 ml) was added sodium hydride (0.19

g, 4.8 mmol) (60% in oil) at 0°C, and the mixture was stirred at 0°C for 10 min. To the obtained mixture was added N-phenyltrifluoromethanesulfonimide (1.71 g, 4.8 mmol) and the mixture was stirred at room temperature  
5 for 3 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column  
10 chromatography to give tert-butyl [4-(4-fluorophenyl)-2-isobutyl-1-oxo-6-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinyl]methylcarbamate (2.02 g, 88.2%) as an oil.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.99 (6H, d, J=6.6 Hz), 1.43 (9H, s),  
15 2.14-2.28 (1H, m), 4.07 (2H, d, J=7.6 Hz), 4.22 (2H, d, J=5.8 Hz), 4.47 (1H, bs), 6.80 (1H, d, J=2.4 Hz), 7.22-7.44 (5H, m), 8.55 (1H, d, J=8.6 Hz).

(2) A suspension of tert-butyl [4-(4-fluorophenyl)-2-isobutyl-1-oxo-6-trifluoromethanesulfonyloxy-1,2-  
20 dihydro-3-isoquinolinyl]methylcarbamate (2.00 g, 3.5 mmol), butyl acrylate (0.76 ml, 5.3 mmol), sodium hydrogencarbonate (0.45 g, 5.5 mmol), tetrabutylammonium chloride (0.11 g, 0.4 mmol) and palladium acetate (90 mg, 0.4 mmol) in N,N-dimethylformamide (30 ml) was stirred  
25 with heating at 100°C under an argon atmosphere for 24 h.

The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced  
30 pressure. The residue was purified by silica gel column chromatography to give butyl (E)-3-[3-[(tert-butoxycarbonyl)amino]methyl]-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propionate as an amorphous.

35 <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.95 (3H, t, J=7.7 Hz), 1.00 (6H, d, J=6.6 Hz), 1.34-1.47 (11H, m), 1.62-1.72 (2H, m), 2.18-

2.28 (1H, m), 4.06 (2H, d, J=7.8 Hz), 4.13-4.21 (4H, m), 4.50 (1H, bs), 6.39 (1H, d, J=16.5 Hz), 6.98 (1H, d, J=1.6 Hz), 7.19-7.27 (4H, m), 7.55 (1H, d, J=16.5 Hz), 7.62 (1H, dd, J=1.6, 8.7 Hz), 8.44 (1H, d, J=8.7 Hz).

5 (3) To a solution of butyl (E)-3-[3-[[[tert-butoxycarbonyl)amino]methyl]-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenate (0.56 g, 1 mmol) in tetrahydrofuran (10 ml) and methanol (10 ml) was added 1N sodium hydroxide (2 ml). The  
10 obtained mixture was stirred at room temperature for 1 h.

The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under

15 reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give (E)-3-[3-[[[tert-butoxycarbonyl)amino]methyl]-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenic acid (0.36 g, 72.0%) as  
20 crystals.

Melting point 201-202°C.

Elemental analysis for  $C_{28}H_{31}N_2O_5F \cdot 0.25H_2O$

Calculated: C, 67.39; H, 6.36; N, 5.61.

Found: C, 67.69; H, 6.27; N, 5.49.

25  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (6H, d, J=6.4 Hz), 1.49 (9H, s), 2.11-2.24 (1H, m), 4.04 (2H, d, J=7.2 Hz), 4.13 (2H, d, J=3.0 Hz), 5.74 (1H, bs), 6.28 (1H, d, J=16.4 Hz), 6.77 (1H, s), 7.21-7.34 (5H, m), 7.43 (1H, d, J=16.4 Hz), 8.22 (1H, d, J=8.2 Hz).

30 (4) A solution of (E)-3-[3-[[[tert-butoxycarbonyl)amino]methyl]-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenic acid (0.20 g, 0.4 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.15 g,  
35 0.8 mmol) and 1-hydroxybenzotriazole ammonium salt (0.12 g, 0.8 mmol) in N,N-dimethylformamide (10 ml) was

stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give (E)-3-[3-[[tert-butoxycarbonyl)amino]methyl]-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide (0.13 g, 65.0%) as crystals.

Melting point 161-163°C.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.00 (6H, d, J=6.6 Hz), 1.44 (9H, s), 2.16-2.24 (1H, m), 4.07 (2H, d, J=7.4 Hz), 4.19 (2H, d, J=5.6 Hz), 4.96 (1H, bs), 5.75 (1H, bs), 6.38 (1H, d, J=15.6 Hz), 6.94 (1H, s), 7.26-7.30 (2H, m), 7.40-7.56 (5H, m), 8.29 (1H, d, J=8.4 Hz).

(5) (E)-3-[3-[[tert-butoxycarbonyl)amino]methyl]-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide (0.10 g, 0.2 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate to give (E)-3-[3-(aminomethyl)-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide hydrochloride (0.08 g, 88.8%) as crystals.

Melting point 255-258°C.

Elemental analysis for C<sub>23</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub>ClF 0.75H<sub>2</sub>O

Calculated: C, 62.30; H, 6.02; N, 9.48.

Found: C, 61.90; H, 6.38; N, 9.31.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.92 (6H, d, J=6.6 Hz), 1.99-2.19 (1H, m), 3.86 (2H, d, J=4.0 Hz), 4.08 (2H, d, J=7.0 Hz), 6.57 (1H, d, J=15.8 Hz), 7.00 (1H, d, J=1.6 Hz), 7.18 (1H, bs), 7.32-7.51 (5H, m), 7.67 (1H, bs), 7.78 (1H, dd, J=1.6, 8.4 Hz), 8.35 (1H, d, J=8.4 Hz), 8.61 (3H, bs).

Example 181

2-[[3-(Aminomethyl)-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinyloxy]acetamide hydrochloride  
(1) A mixture of methyl 6-benzyloxy-2-isobutyl-1-oxo-4-trifluoromethanesulfonyloxy-1,2-dihydro-3-

- 5 isoquinolinecarboxylate (9.24 g, 18 mmol), 4-methylphenylboronic acid (2.94 g, 21.6 mmol) and sodium carbonate (2.86 g, 27 mmol) in toluene (50 ml) - methanol (10 ml) - water (10 ml) was stirred under an argon atmosphere at room temperature for 30 min. To the  
10 obtained mixture was added tetrakis(triphenylphosphine)palladium (1.04 g, 1 mmol) and the mixture was refluxed under heating under an argon atmosphere for 10 h. The reaction mixture was poured into water and extracted with ethyl acetate.  
15 After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give methyl 6-benzyloxy-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-  
20 dihydro-3-isoquinolinecarboxylate (6.91 g, 84.4%) as crystals.

Melting point 142.5-143°C.

Elemental analysis for  $C_{29}H_{29}NO_4$

Calculated: C, 76.46; H, 6.42; N, 3.07.

- 25 Found: C, 76.35; H, 6.40; N, 2.86.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.92 (6H, d,  $J=6.6$  Hz), 2.04-2.20 (1H, m), 2.43 (3H, s), 3.47 (3H, s), 3.93 (2H, d,  $J=7.6$  Hz), 4.97 (2H, s), 6.65 (1H, d,  $J=2.6$  Hz), 7.11-7.37 (10H, m), 8.42 (1H, d,  $J=8.8$  Hz).

- 30 (2) To a suspension of methyl 6-benzyloxy-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (6.83 g, 15 mmol) in methanol (50 ml) was added an aqueous solution (20 ml) of lithium hydroxide monohydrate (1.89 g, 45 mmol). The obtained  
35 mixture was refluxed under heating for 24 h. The reaction mixture was poured into water, acidified with

1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals was recrystallized from  
5 ethyl acetate - diisopropyl ether to give 6-benzyloxy-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (5.78 g, 87.3%) as crystals. Melting point 153-154°C.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.85 (6H, d, J=6.6 Hz), 2.03-2.21 (1H,  
10 m), 2.42 (3H, s), 3.86 (2H, d, J=7.4 Hz), 4.13 (1H, bs), 4.96 (2H, s), 6.61 (1H, d, J=2.4 Hz), 7.10 (1H, dd, J=2.4, 9.0 Hz), 7.13-7.36 (9H, m), 8.28 (1H, d, J=9.0 Hz).

(3) To a mixed solution of 6-benzyloxy-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic  
15 acid (5.74 g, 13 mmol) in tetrahydrofuran (50 ml) were added oxalyl chloride (1.4 ml, 15.6 mmol) and N,N-dimethylformamide (3 drops), and the mixture was stirred at room temperature for 1 h. The reaction mixture was  
20 concentrated under reduced pressure and the residue was dissolved in tetrahydrofuran (20 ml). The obtained solution was added dropwise to a suspension of sodium tetrahydroborate (1.72 g, 45.5 mmol) in 1,2-dimethoxyethane (50 ml) at 0°C. The obtained mixture was  
25 stirred at 0°C for 1 h. The reaction mixture was poured into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were  
30 recrystallized from ethyl acetate - diisopropyl ether to give 6-benzyloxy-3-hydroxymethyl-2-isobutyl-4-(4-methylphenyl)-1(2H)-isoquinolinone (4.41 g, 79.5%) as crystals.

Melting point 74-76°C.

35 <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.95 (6H, d, J=6.6 Hz), 2.16-2.26 (1H, m), 2.41 (1H, bs), 2.47 (3H, s), 4.17 (2H, d, J=7.5 Hz),

4.43 (2H, s), 4.89 (2H, s), 6.39 (1H, d, J=2.4 Hz), 6.98 (1H, dd, J=2.4, 8.8 Hz), 7.17 (2H, d, J=7.8 Hz), 7.23-7.34 (7H, m), 8.28 (1H, d, J=8.8 Hz).

(4) To a suspension of 6-benzyloxy-3-hydroxymethyl-2-isobutyl-4-(4-methylphenyl)-1(2H)-isoquinolinone (4.28 g, 10 mmol) in toluene (50 ml) was added thionyl chloride (1.5 ml, 20 mmol). The obtained mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 6-benzyloxy-3-chloromethyl-2-isobutyl-4-(4-methylphenyl)-1(2H)-isoquinolinone (4.26 g, 95.5%) as an oil.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.99 (6H, d, J=7.0 Hz), 2.14-2.30 (1H, m), 2.47 (3H, s), 4.15 (2H, d, J=6.8 Hz), 4.39 (2H, s), 4.93 (2H, s), 6.45 (1H, d, J=2.6 Hz), 7.09-7.35 (10H, m), 8.40 (1H, d, J=8.8 Hz).

(5) A solution of 6-benzyloxy-3-chloromethyl-2-isobutyl-4-(4-methylphenyl)-1(2H)-isoquinolinone (4.24 g, 9.5 mmol) and potassium phthalimide (2.65 g, 14.3 mmol) in N,N-dimethylformamide (50 ml) was stirred at room temperature for 6 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 2-[[6-benzyloxy-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-3-isoquinolinyl]methyl]-1H-isoindole-1,3(2H)-dione (5.07 g, 96.0%) as crystals.

Melting point 158-159°C.

Elemental analysis for  $\text{C}_{36}\text{H}_{32}\text{N}_2\text{O}_4$

Calculated: C, 77.68; H, 5.79; N, 5.03.

Found: C, 77.89; H, 5.91; N, 4.96.



<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.98 (6H, d, J=6.6 Hz), 2.14-2.28 (1H, m), 2.38 (3H, s), 4.01 (2H, d, J=7.2 Hz), 4.78 (2H, s), 4.92 (2H, s), 6.41 (1H, d, J=2.6 Hz), 7.09 (1H, dd, J=2.6, 8.8 Hz), 7.12-7.19 (4H, m), 7.20-7.35 (5H, m),  
5 7.66-7.76 (4H, m), 8.38 (1H, d, J=8.8 Hz).

(6) To a suspension of 2-[[6-benzyloxy-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-3-isoquinolinyl]methyl]-1H-isoindole-1,3(2H)-dione (5.01 g, 9 mmol) in ethanol (50 ml) was added hydrazine monohydrate (1.3 ml, 27  
10 mmol). The obtained mixture was refluxed under heating for 1 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated  
15 under reduced pressure. The residue was dissolved in tetrahydrofuran (50 ml) and di-t-butyl dicarbonate (3.1 ml, 13.5 mmol) was added thereto. The obtained mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl  
20 acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl [6-benzyloxy-2-isobutyl-4-(4-  
25 methylphenyl)-1-oxo-1,2-dihydro-3-isoquinolinyl]-methylcarbamate (4.48 g, 94.5%) as crystals.

Melting point 164-164.5°C.

Elemental analysis for C<sub>33</sub>H<sub>38</sub>N<sub>2</sub>O<sub>4</sub>

Calculated: C, 75.26; H, 7.27; N, 5.32.

30 Found: C, 75.17; H, 7.39; N, 5.17.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.98 (6H, d, J=7.0 Hz), 1.42 (9H, s), 2.13-2.27 (1H, m), 2.46 (3H, s), 4.03 (2H, d, J=7.2 Hz), 4.18 (2H, d, J=5.4 Hz), 4.48 (1H, bs), 4.92 (2H, s), 6.38 (1H, d, J=2.6 Hz), 7.05-7.11 (3H, m), 7.22-7.35 (7H,  
35 m), 8.37 (1H, d, J=8.8 Hz).

(7) A suspension of tert-butyl [6-benzyloxy-2-isobutyl-

4-(4-methylphenyl)-1-oxo-1,2-dihydro-3-  
isoquinolinyl]methylcarbamate (4.21 g, 8 mmol) and 5%  
palladium carbon (2.0 g) in ethanol (20 ml) and  
tetrahydrofuran (20 ml) was stirred under a hydrogen  
5 atmosphere at room temperature for 2 h. The catalyst  
was filtered off and the filtrate was concentrated under  
reduced pressure. The residue was purified by silica  
gel column chromatography to give tert-butyl [6-hydroxy-  
2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-3-  
10 isoquinolinyl]methylcarbamate (3.28 g, 94.0%) as  
crystals.

Melting point 233-234°C.

Elemental analysis for  $C_{26}H_{32}N_2O_4$ .

Calculated: C, 71.53; H, 7.39; N, 6.42.

15 Found: C, 71.35; H, 7.35; N, 6.22.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.96 (6H, d,  $J=6.6$  Hz), 1.41 (9H, s),  
2.12-2.26 (1H, m), 2.41 (3H, s), 4.02 (2H, d,  $J=7.4$  Hz),  
4.19 (2H, d,  $J=5.4$  Hz), 4.46 (1H, bs), 6.39 (1H, d,  
 $J=2.2$  Hz), 7.04 (1H, dd,  $J=2.2, 8.8$  Hz), 7.08 (2H, d,  
20  $J=8.4$  Hz), 7.24 (2H, d,  $J=8.4$  Hz), 7.73 (1H, bs), 8.28  
(1H, d,  $J=8.8$  Hz).

(8) A solution of tert-butyl [6-hydroxy-2-isobutyl-4-(4-  
methylphenyl)-1-oxo-1,2-dihydro-3-  
isoquinolinyl]methylcarbamate (0.44 g, 1 mmol), 2-  
25 iodoacetamide (0.37 g, 2 mmol) and 1,8-  
diazabicyclo[5.4.0]-7-undecene (0.30 ml, 2 mmol) in N,N-  
dimethylacetamide (10 ml) was stirred at 80°C for 12 h.  
The reaction mixture was poured into water and extracted  
with ethyl acetate. The extract was washed with brine,  
30 dried over anhydrous magnesium sulfate and concentrated  
under reduced pressure. The residue was purified by  
silica gel column chromatography to give tert-butyl [6-  
(2-amino-2-oxoethoxy)-2-isobutyl-4-(4-methylphenyl)-1-  
oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.18 g,  
35 36.7%) as crystals.

Melting point 239-239.5°C.

Elemental analysis for  $C_{28}H_{35}N_3O_5$

Calculated: C, 68.13; H, 7.15; N, 8.51.

Found: C, 67.77; H, 7.09; N, 8.21.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (6H, d,  $J=6.6$  Hz), 1.43 (9H, s),  
5 2.15-2.29 (1H, m), 2.47 (3H, s), 4.05 (2H, d,  $J=7.6$  Hz),  
4.19 (2H, d,  $J=5.4$  Hz), 4.33 (2H, s), 4.48 (1H, bs),  
5.69 (1H, bs), 6.34 (1H, d,  $J=2.6$  Hz), 6.52 (1H, bs),  
7.04 (1H, dd,  $J=2.6, 9.0$  Hz), 7.10 (2H, d,  $J=7.9$  Hz),  
7.31 (2H, d,  $J=7.9$  Hz), 8.42 (1H, d,  $J=9.0$  Hz).

10 (9) Tert-butyl [6-(2-amino-2-oxoethoxy)-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.15 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room  
15 temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from ethyl acetate - diisopropyl ether to give 2-[[3-(aminomethyl)-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-  
20 isoquinolinyl]oxy]acetamide hydrochloride (0.11 g, 91.7%) as crystals.

Melting point 278-280°C.

Elemental analysis for  $C_{23}H_{28}N_3O_3 \cdot 0.5H_2O$

Calculated: C, 62.93; H, 6.66; N, 9.57.

25 Found: C, 62.97; H, 6.53; N, 9.28.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.90 (6H, d,  $J=6.6$  Hz), 1.99-2.16 (1H, m), 2.43 (3H, s), 3.86 (2H, s), 4.04 (2H, d,  $J=7.0$  Hz), 4.36 (2H, s), 6.34 (1H, d,  $J=2.6$  Hz), 7.19 (1H, dd,  $J=2.6, 8.8$  Hz), 7.25 (2H, d,  $J=8.2$  Hz), 7.35 (1H, bs),  
30 7.37 (2H, d,  $J=8.2$  Hz), 7.57 (1H, bs), 8.27 (1H, d,  $J=8.8$  Hz), 8.48 (3H, s).

#### Example 182

3-(Aminomethyl)-2-isobutyl-4-(4-methylphenyl)-1(2H)-isoquinolinone-6-carboxamide hydrochloride

35 (1) To a solution of tert-butyl [6-hydroxy-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-3-

isoquinolinyl)methylcarbamate (Example 181(7)) (2.18 g, 5 mmol) in N,N-dimethylformamide (20 ml) was added sodium hydride (0.30 g, 8.3 mmol) (60% in oil) at 0°C and the mixture was stirred at 0°C for 30 min. To the  
5 obtained mixture was added N-phenyltrifluoromethanesulfonimide (2.68 g, 8.3 mmol) and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with  
10 water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [2-isobutyl-4-(4-methylphenyl)-1-oxo-6-trifluoromethanesulfonyloxy-1,2-dihydro-3-  
15 isoquinolinyl)methylcarbamate (2.85 g, 100%) as an oil.  
<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.99 (6H, d, J=7.0 Hz), 1.43 (9H, s), 2.14-2.27 (1H, m), 2.47 (3H, s), 4.09 (2H, d, J=7.4 Hz), 4.24 (2H, d, J=5.8 Hz), 4.45 (1H, t, J=2.6 Hz), 6.86 (1H, d, J=2.6 Hz), 7.12 (2H, d, J=8.2 Hz), 7.13-7.40 (3H, m),  
20 8.54 (1H, d, J=8.8 Hz).  
(2) A mixture of tert-butyl [2-isobutyl-4-(4-methylphenyl)-1-oxo-6-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinyl)methylcarbamate (2.84 g, 5 mmol), 1,1'-bis(diphenylphosphino)ferrocene (0.14 g, 0.25 mmol),  
25 triethylamine (0.77 ml, 5.5 mmol) and palladium acetate (56 mg, 0.25 mmol) in tetrahydrofuran (20 ml) - methanol (20 ml) was stirred with heating at 100°C under a carbon monoxide atmosphere at 5 atm for 1 h. The reaction mixture was poured into water and extracted with ethyl  
30 acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give methyl 3-[[[(tert-butoxycarbonyl)amino]methyl]-2-  
35 isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinecarboxylate (2.11 g, 88.3%) as crystals.

Melting point 193-194.5°C.

Elemental analysis for  $C_{28}H_{34}N_2O_5$

Calculated: C, 70.27; H, 7.16; N, 5.85.

Found: C, 69.97; H, 7.22; N, 5.71.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.00 (6H, d, J=6.6 Hz), 1.43 (9H, s), 2.17-2.32 (1H, m), 2.47 (3H, s), 3.86 (3H, s), 4.09 (2H, d, J=7.4 Hz), 4.22 (2H, d, J=5.8 Hz), 4.54 (1H, bs), 7.13 (2H, d, J=7.8 Hz), 7.32 (2H, d, J=7.8 Hz), 7.68 (1H, d, J=1.6 Hz), 8.02 (1H, dd, J=1.6, 8.2 Hz), 8.49 (1H, d, J=8.2 Hz).

(3) To a solution of methyl 3-[[[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinecarboxylate (1.91 g, 4 mmol) in tetrahydrofuran (10 ml)-methanol (10 ml) was added 1N sodium hydroxide (8 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran - isopropyl ether to give 3-[[[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid (1.67 g, 90.3%) as crystals.

Melting point 230-231°C.

Elemental analysis for  $C_{27}H_{32}N_2O_5$

Calculated: C, 69.81; H, 6.94; N, 6.03.

Found: C, 69.45; H, 7.09; N, 5.67.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.98 (6H, d, J=6.6 Hz), 1.49 (9H, s), 2.07-2.25 (1H, m), 2.48 (3H, s), 4.05 (2H, d, J=7.4 Hz), 4.18 (2H, d, J=4.4 Hz), 5.75 (1H, bs), 7.21 (2H, d, J=7.8 Hz), 7.32 (2H, d, J=7.8 Hz), 7.48 (1H, s), 7.79 (1H, d, J=8.2 Hz), 8.32 (1H, d, J=8.2 Hz).

(4) A solution of 3-[[[(tert-

butoxycarbonyl)amino]methyl]-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid (0.92 g, 2 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.77 g, 4 mmol), and 1-hydroxybenzotriazole ammonium salt (0.61 g, 4 mmol) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran - diisopropyl ether to give 3-[[ (tert-butoxycarbonyl)amino]methyl]-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide (0.82 g, 89.1%) as crystals. Melting point 225-226°C.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.00 (6H, d, J=6.6 Hz), 1.43 (9H, s), 2.17-2.28 (1H, m), 2.46 (3H, s), 4.08 (2H, d, J=7.2 Hz), 4.22 (2H, d, J=5.6 Hz), 4.52 (1H, bs), 5.62 (1H, bs), 6.00 (1H, bs), 7.12 (2H, d, J=7.8 Hz), 7.32 (2H, d, J=7.8 Hz), 7.42 (1H, d, J=1.8 Hz), 7.78 (1H, dd, J=1.8, 8.4 Hz), 8.49 (1H, d, J=8.4 Hz).

(5) A solution of 3-[[ (tert-butoxycarbonyl)amino]methyl]-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide (0.42 g, 0.9 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol - diethyl ether to give 3-(aminomethyl)-2-isobutyl-4-(4-methylphenyl)-1(2H)-isoquinolinone-6-carboxamide hydrochloride (0.34 g, 94.4%) as crystals.

Melting point 286-288°C.  
Elemental analysis for C<sub>22</sub>H<sub>26</sub>N<sub>3</sub>O<sub>3</sub>Cl 1.25H<sub>2</sub>O

Calculated: C, 62.55; H, 6.80; N, 9.95.

Found: C, 62.66; H, 6.93; N, 9.99.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.92 (6H, d, J=6.6 Hz), 2.02-2.16 (1H, m), 2.45 (3H, s), 3.88 (2H, s), 4.08 (2H, d, J=7.4 Hz),  
5 7.28 (2H, d, J=8.1 Hz), 7.39 (2H, d, J=8.1 Hz), 7.46 (1H, d, J=1.6 Hz), 7.58 (1H, bs), 7.99 (1H, d, J=1.6, 8.2 Hz), 8.16 (1H, bs), 8.36 (1H, d, J=8.2 Hz), 8.49 (3H, bs).

#### Example 183

3-(Aminomethyl)-2-isobutyl-4-(4-methylphenyl)-1(2H)-  
10 isoquinolinone-6-carbonitrile hydrochloride

(1) A solution of 3-[[tert-butoxycarbonyl]amino]methyl]-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide (Example 3 (4)) (0.37 g, 0.8  
15 mmol) and cyanuric chloride (0.44 g, 2.4 mmol) in N,N-dimethylformamide (10 mmol) was stirred at 0°C for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated  
20 under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [6-cyano-4-(4-methylphenyl)-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.32 g, 91.4%) as crystals.

25 Melting point 156-157°C.

Elemental analysis for C<sub>27</sub>H<sub>31</sub>N<sub>3</sub>O<sub>3</sub>

Calculated: C, 72.78; H, 7.01; N, 9.43.

Found: C, 72.66; H, 7.16; N, 9.46.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.00 (6H, d, J=6.6 Hz), 1.43 (9H, s),  
30 2.14-2.29 (1H, m), 2.48 (3H, s), 4.09 (2H, d, J=7.6 Hz), 4.24 (2H, d, J=5.8 Hz), 4.45 (1H, bs), 7.10 (2H, d, J=7.7 Hz), 7.31 (1H, d, J=1.4 Hz), 7.35 (2H, d, J=7.7 Hz), 7.63 (1H, dd, J=1.4, 8.2 Hz), 8.53 (1H, d, J=8.2 Hz).

35 (2) Tert-butyl [6-cyano-4-(4-methylphenyl)-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.27 g, 0.6

mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol - diethyl ether to give 3-(aminomethyl)-2-isobutyl-4-(4-methylphenyl)-1(2H)-isoquinolinone-6-carbonitrile hydrochloride (0.22 g, 95.7%) as crystals.

Melting point 278-279°C.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.92 (6H, d, J=6.6 Hz), 1.99-2.16 (1H, m), 2.45 (3H, s), 3.90 (2H, s), 4.11 (2H, d, J=7.0 Hz), 7.25 (1H, d, J=1.4 Hz), 7.31 (2H, d, J=7.9 Hz), 7.41 (2H, d, J=7.9 Hz), 7.96 (1H, dd, J=1.4, 8.4 Hz), 8.47 (1H, d, J=8.4 Hz), 8.65 (3H, bs).

**Example 184**

(E)-3-[3-(Aminomethyl)-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide hydrochloride

(1) A suspension of tert-butyl [2-isobutyl-4-(4-methylphenyl)-1-oxo-6-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinyl]methylcarbamate (Example 182 (1)) (1.42 g, 2.5 mmol), butyl acrylate (0.54 ml, 3.8 mmol), sodium hydrogencarbonate (0.32 g, 3.8 mmol), tetrabutylammonium chloride (83 mg, 0.3 mmol) and palladium acetate (67 mg, 0.3 mmol) in N,N-dimethylformamide (30 ml) was stirred with heating at 100°C under an argon atmosphere for 20 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give butyl (E)-3-[3-[[tert-butoxycarbonyl]amino]methyl]-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenate (0.56 g, 40.3%) as an amorphous.



<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.95 (3H, t, J=7.8 Hz), 1.00 (6H, d, J=6.6 Hz), 1.35-1.47 (11H, m), 1.62-1.71 (2H, m), 2.18-2.29 (1H, m), 2.49 (3H, s), 4.08 (2H, d, J=6.0 Hz), 4.18 (2H, t, J=6.6 Hz), 4.22 (2H, d, J=4.8 Hz), 4.52 (1H, bs),  
5 6.38 (1H, d, J=15.9 Hz), 7.04 (1H, d, J=1.0 Hz), 7.13 (2H, d, J=8.1 Hz), 7.33 (2H, d, J=8.1 Hz), 7.55 (1H, d, J=15.9 Hz), 7.61 (1H, dd, J=1.0, 8.4 Hz), 8.44 (1H, d, J=8.4 Hz).

(2) To a solution of butyl ((E)-3-[3-[[[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenate (0.50 g, 0.9 mmol) in tetrahydrofuran (10 ml)-methanol (10 ml) was added 1N sodium hydroxide (2 ml). The obtained mixture was stirred at room temperature for  
15 1 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were  
20 recrystallized from ethyl acetate - diisopropyl ether to give (E)-3-[3-[[[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenic acid (0.38 g, 84.4%) as crystals.

25 Melting point 171-173°C.

Elemental analysis for C<sub>29</sub>H<sub>34</sub>N<sub>2</sub>O<sub>5</sub> · 0.25H<sub>2</sub>O

Calculated: C, 70.35; H, 7.02; N, 5.66.

Found: C, 70.16; H, 6.94; N, 5.49.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.99 (6H, d, J=6.6 Hz), 1.48 (9H, s),  
30 2.08-2.29 (1H, m), 2.50 (3H, s), 4.05 (2H, d, J=6.3 Hz), 4.17 (2H, d, J=4.5 Hz), 5.46 (1H, bs), 6.30 (1H, d, J=15.9 Hz), 6.88 (1H, s), 7.20 (2H, d, J=7.6 Hz), 7.34 (2H, d, J=7.6 Hz), 7.41 (1H, d, J=8.6 Hz), 7.47 (1H, d, J=15.9 Hz), 8.29 (1H, d, J=8.6 Hz).

35 (3) A solution of (E)-3-[3-[[[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-4-(4-

- 5 methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenic acid (0.25 g, 0.5 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.19 g, 1 mmol) and 1-hydroxybenzotriazole ammonium salt (0.15 g, 1 mmol) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give (E)-3-[3-[[tert-butoxycarbonyl]amino]methyl]-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide (0.21 g, 84.0%) as crystals.
- 10  
15 Melting point 152-154°C.  
Elemental analysis for  $C_{29}H_{35}N_3O_4 \cdot 0.75H_2O$   
Calculated: C, 69.23; H, 7.31; N, 8.35.  
Found: C, 69.58; H, 7.29; N, 8.01.  
 $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.00 (6H, d,  $J=6.6$  Hz), 1.43 (9H, s),  
20 2.16-2.28 (1H, m), 2.48 (3H, s), 4.07 (2H, d,  $J=7.4$  Hz),  
4.22 (2H, d,  $J=5.6$  Hz), 4.70 (1H, bs), 5.71 (2H, bs),  
6.40 (1H, d,  $J=15.6$  Hz), 7.00 (1H, s), 7.12 (2H, d,  $J=7.8$  Hz), 7.32 (2H, d,  $J=7.8$  Hz), 7.44-7.54 (2H, m),  
8.36 (1H, d,  $J=8.4$  Hz).
- 25 (4) (E)-3-[3-[[tert-butoxycarbonyl]amino]methyl]-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide (0.15 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room  
30 temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate - diisopropyl ether to give (E)-3-[3-(aminomethyl)-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide hydrochloride (0.12 g, 92.3%) as crystals.  
35 Melting point 264-266°C.

Elemental analysis for  $C_{24}H_{28}N_3O_2Cl \cdot 1.25H_2O$

Calculated: C, 64.28; H, 6.85; N, 9.37.

Found: C, 64.37; H, 6.88; N, 9.08.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.92 (6H, d, J=6.6 Hz), 2.04-2.16 (1H, m), 3.87 (2H, d, J=2.4 Hz), 4.08 (2H, d, J=6.9 Hz), 6.56 (1H, d, J=15.9 Hz), 7.00 (1H, d, J=1.2 Hz), 7.18 (1H, bs), 7.25-7.42 (5H, m), 7.67 (1H, bs), 7.77 (1H, dd, J=1.2, 8.7 Hz), 8.34 (1H, d, J=8.7 Hz), 8.53 (3H, bs).

**Example 185**

10 2-[[3-(Aminomethyl)-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]oxy]acetamide hydrochloride

(1) A mixed solution of methyl 6-benzyloxy-2-isobutyl-1-oxo-4-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinecarboxylate (10.27 g, 20 mmol), 4-chlorophenylboronic acid (3.75 g, 24 mmol) and sodium carbonate (5.30 g, 50 mmol) in toluene (50 ml)-methanol (10 ml)-water (10 ml) was stirred under an argon atmosphere at room temperature for 30 min. To the obtained mixture was added

20 tetrakis(triphenylphosphine)palladium (1.15 g, 1 mmol) and the mixture was refluxed under heating under an argon atmosphere for 10 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give methyl 6-benzyloxy-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate (5.21 g, 54.8%) as crystals.

Melting point 165.5-166°C.

Elemental analysis for  $C_{28}H_{26}NO_4Cl$

Calculated: C, 70.66; H, 5.51; N, 2.94.

Found: C, 70.89; H, 5.68; N, 2.78.

35  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.91 (6H, d, J=7.0 Hz), 2.03-2.21 (1H, m), 3.50 (3H, s), 3.93 (2H, d, J=7.8 Hz), 4.99 (2H, s),

6.52 (1H, d, J=2.6 Hz), 7.15-7.22 (3H, m), 7.26-7.44 (7H, m), 8.42 (1H, d, J=8.8 Hz).

(2) To a suspension of methyl 6-benzyloxy-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-  
5 isoquinolinecarboxylate (5.00 g, 10.5 mmol) in 1,4-dioxane (50 ml) was added an aqueous solution (20 ml) of lithium hydroxide monohydrate (1.32 g, 31.5 mmol). The obtained mixture was refluxed under heating for 24 h. The reaction mixture was poured into water, acidified  
10 with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran - n-hexane to give  
15 6-benzyloxy-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (4.69 g, 96.7%) as crystals.

Melting point 200-201°C.

Elemental analysis for  $C_{27}H_{24}NO_4Cl$

20 Calculated: C, 70.20; H, 5.24; N, 3.03.

Found: C, 70.12; H, 5.28; N, 2.97.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.86 (6H, d, J=6.6 Hz), 2.07-2.25 (1H, m), 3.90 (2H, d, J=7.2 Hz), 5.00 (2H, s), 6.51 (1H, d, J=2.4 Hz), 7.14 (1H, dd, J=2.4, 9.0 Hz), 7.21-7.40 (9H, m), 8.25 (1H, d, J=9.0 Hz).  
25

(3) To a mixture of 6-benzyloxy-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylic acid (4.62 g, 10 mmol) and tetrahydrofuran (50 ml) were added oxalyl chloride (1.0 ml, 15.6 mmol) and N,N-  
30 dimethylformamide (3 drops), and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in tetrahydrofuran (20 ml). The obtained solution was added dropwise to a suspension of sodium  
35 tetrahydroborate (1.32 g, 35 mmol) in 1,2-dimethoxyethane (30 ml) at 0°C. The obtained mixture was

stirred at 0°C for 1 h. The reaction mixture was poured into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give 6-benzyloxy-4-(4-chlorophenyl)-3-hydroxymethyl-2-isobutyl-1(2H)-isoquinolinone (4.31 g, 96.4%) as crystals.

10 Melting point 87-88°C.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.95 (6H, d, J=6.6 Hz), 2.11-2.28 (1H, m), 2.39 (1H, bs), 4.16 (2H, d, J=7.6 Hz), 4.41 (2H, d, J=5.4 Hz), 4.92 (2H, s), 6.29 (1H, d, J=2.4 Hz), 7.00 (1H, dd, J=2.4, 9.0 Hz), 7.21-7.38 (7H, m), 7.45 (2H, d, J=8.4 Hz), 8.27 (1H, d, J=8.8 Hz).

(4) To a suspension of 6-benzyloxy-4-(4-chlorophenyl)-3-hydroxymethyl-2-isobutyl-1(2H)-isoquinolinone (4.25 g, 9.5 mmol) in toluene (50 ml) was added thionyl chloride (1.4 ml, 19 mmol). The obtained mixture was refluxed under heating for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 6-benzyloxy-3-chloromethyl-4-(4-chlorophenyl)-2-isobutyl-1(2H)-isoquinolinone (3.98 g, 89.8%) as an oil.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.99 (6H, d, J=7.0 Hz), 2.13-2.30 (1H, m), 4.14 (2H, d, J=7.6 Hz), 4.34 (2H, s), 4.96 (2H, s), 6.34 (1H, d, J=2.2 Hz), 7.06-7.38 (8H, m), 7.44-7.50 (2H, m), 8.41 (1H, d, J=8.8 Hz).

(5) A solution of 6-benzyloxy-3-chloromethyl-4-(4-chlorophenyl)-2-isobutyl-1(2H)-isoquinolinone (3.96 g, 8.5 mmol) and potassium phthalimide (2.37 g, 12.8 mmol) in N,N-dimethylformamide (40 ml) was stirred at room temperature for 6 h. The reaction mixture was poured into water and extracted with ethyl acetate. After

washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 2-[[6-benzyloxy-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methyl]-1H-isoindole-1,3(2H)-dione (4.72 g, 96.3%) as crystals.

Melting point 182-183°C.

Elemental analysis for  $C_{35}H_{29}N_2O_4Cl$

10 Calculated: C, 72.85; H, 5.07; N, 4.85.

Found: C, 72.95; H, 5.19; N, 4.70.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.98 (6H, d,  $J=6.6$  Hz), 2.09-2.31 (1H, m), 4.00 (2H, d,  $J=7.2$  Hz), 4.74 (2H, s), 4.93 (2H, s), 6.29 (1H, d,  $J=2.6$  Hz), 7.11 (1H, dd,  $J=2.6, 8.8$  Hz), 7.19-7.41 (9H, m), 7.66-7.79 (4H, m), 8.38 (1H, d,  $J=8.8$  Hz).

(6) To a suspension of 2-[[6-benzyloxy-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methyl]-1H-isoindole-1,3(2H)-dione (4.61 g, 8 mmol) in ethanol (50 ml) was added hydrazine monohydrate (1.2 ml, 24 mmol). The obtained mixture was refluxed under heating for 1 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (50 ml) and di-*t*-butyl dicarbonate (2.8 ml, 12 mmol) was added thereto. The obtained mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give *tert*-butyl [6-benzyloxy-4-(4-chlorophenyl)-2-

isobutyl-1-oxo-1,2-dihydro-3-  
isoquinolinyl]methylcarbamate (4.16 g, 95.2%) as  
crystals.

Melting point 186-187°C.

5 Elemental analysis for  $C_{32}H_{35}N_2O_4Cl$

Calculated: C, 70.25; H, 6.45; N, 5.12.

Found: C, 70.17; H, 6.43; N, 5.00.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.98 (6H, d,  $J=6.6$  Hz), 1.42 (9H, s),  
2.14-2.28 (1H, m), 4.02 (2H, d,  $J=7.6$  Hz), 4.15 (2H, d,  
10  $J=5.2$  Hz), 4.46 (1H, bs), 4.95 (2H, s), 6.28 (1H, d,  
 $J=2.6$  Hz), 7.07-7.16 (3H, m), 7.22-7.37 (5H, m), 7.42-  
7.49 (2H, m), 8.37 (1H, d,  $J=8.8$  Hz).

(7) Tert-butyl [6-benzyloxy-4-(4-chlorophenyl)-2-  
isobutyl-1-oxo-1,2-dihydro-3-

15 isoquinolinyl]methylcarbamate (0.54 g, 1 mmol) was  
suspended in 48% aqueous solution (20 ml) of hydrogen  
bromide and the obtained mixture was refluxed under  
heating for 3 h. The reaction mixture was neutralized  
with 1N sodium hydroxide aqueous solution and extracted  
20 with ethyl acetate. The extract was washed with brine,  
dried over anhydrous magnesium sulfate and concentrated  
under reduced pressure. The residue was dissolved in  
tetrahydrofuran (10 ml) and di-*t*-butyl dicarbonate (0.28  
ml, 1 mmol) was added thereto. The obtained mixture was  
25 stirred at room temperature for 1 h. The reaction  
mixture was poured into water and extracted with ethyl  
acetate. The extract was washed with brine, dried over  
anhydrous magnesium sulfate and concentrated under  
reduced pressure. The residue was purified by silica  
30 gel column chromatography to give tert-butyl [4-(4-  
chlorophenyl)-6-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-  
isoquinolinyl]methylcarbamate (0.32 g, 71.1%) as  
crystals.

Melting point 220-221°C.

35  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.95 (6H, d,  $J=6.6$  Hz), 1.42 (9H, s),  
2.08-2.29 (1H, m), 4.01 (2H, d,  $J=7.0$  Hz), 4.13 (2H, d,

J=5.6 Hz), 4.50 (1H, bs), 6.33 (1H, d, J=2.4 Hz), 7.03 (1H, dd, J=2.4, 8.8 Hz), 7.03 (2H, d, J=8.2 Hz), 7.40 (2H, d, J=8.2 Hz), 7.93 (1H, bs), 8.26 (1H, d, J=8.8 Hz).

(8) To a solution of tert-butyl [4-(4-chlorophenyl)-6-hydroxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.45 g, 1 mmol) in N,N-dimethylformamide (10 ml) was added sodium hydride (48 mg, 1.2 mmol) (60% in oil) at 0°C, and the mixture was stirred at 0°C for 10 min. To the obtained mixture was added 2-iodoacetamide (0.22 g, 1.2 mmol) and the mixture was stirred at 0°C for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [6-(2-amino-2-oxoethoxy)-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.27 g, 52.9%) as crystals.

Melting point 241-242°C.

Elemental analysis for  $C_{27}H_{32}N_3O_5Cl$

Calculated: C, 63.09; H, 6.27; N, 8.17.

Found: C, 63.07; H, 6.32; N, 8.22.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (6H, d, J=6.6 Hz), 1.43 (9H, s), 2.10-2.28 (1H, m), 4.04 (2H, d, J=7.4 Hz), 4.17 (2H, d, J=5.4 Hz), 4.35 (2H, s), 4.56 (1H, bs), 5.79 (1H, bs), 6.28 (1H, d, J=2.4 Hz), 6.50 (1H, bs), 7.04 (1H, dd, J=2.4, 9.0 Hz), 7.17-7.24 (2H, m), 7.47-7.53 (2H, m), 8.41 (1H, d, J=9.0 Hz).

(9) Tert-butyl [6-(2-amino-2-oxoethoxy)-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.20 g, 0.4 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the



precipitated crystals were recrystallized from ethyl acetate - diisopropyl ether to give 2-[[3-(aminomethyl)-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]oxy]acetamide hydrochloride (0.16 g,

5 88.9%) as crystals.

Melting point 260-262°C.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.91 (6H, d, J=6.6 Hz), 1.99-2.18 (1H, m), 3.84 (2H, bs), 4.03 (2H, d, J=7.4 Hz), 4.39 (2H, s), 6.31 (1H, d, J=2.4 Hz), 7.21 (1H, dd, J=2.4, 9.0 Hz),  
10 7.36 (1H, bs), 7.40 (2H, d, J=8.4 Hz), 7.59 (1H, bs), 7.62 (2H, d, J=8.4 Hz), 8.27 (1H, d, J=9.0 Hz), 8.51 (3H, s).

#### Example 186

3-(Aminomethyl)-4-(4-chlorophenyl)-2-isobutyl-1(2H)-  
15 isoquinolinone-6-carboxamide hydrochloride

(1) To a solution of tert-butyl [6-hydroxy-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (Example 185(7)) (1.83 g, 4 mmol) in N,N-dimethylformamide (20 ml) was added  
20 sodium hydride (0.24 g, 6 mmol) (60% in oil) at 0°C, and the mixture was stirred at 0°C for 10 min. To the obtained mixture was added N-

phenyltrifluoromethanesulfonimide (2.14 g, 6 mmol) and the mixture was stirred at room temperature for 2 h.

25 The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography  
30 to give tert-butyl [4-(4-chlorophenyl)-2-isobutyl-1-oxo-6-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinyl]methylcarbamate (2.36 g, 100%) as an oil.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.98 (6H, d, J=7.0 Hz), 1.43 (9H, s), 2.04-2.26 (1H, m), 4.07 (2H, d, J=7.4 Hz), 4.21 (2H, d, J=5.4 Hz), 4.50 (1H, bs), 6.81 (1H, d, J=2.6 Hz), 7.17-7.26 (2H, m), 7.50-7.57 (3H, m), 8.54 (1H, d, J=8.8 Hz).

(2) A mixed solution of tert-butyl [4-(4-chlorophenyl)-2-isobutyl-1-oxo-6-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinyl]methylcarbamate (2.35 g, 4 mmol), 1,1'-bis(diphenylphosphino)ferrocene (0.11 g, 0.2 mmol),  
5 triethylamine (0.6 ml, 4.4 mmol) and palladium acetate (45 mg, 0.2 mmol) in tetrahydrofuran (20 ml)-methanol (20 ml) was stirred with heating at 100°C under a carbon monoxide atmosphere at 5 atm for 2 h. The reaction mixture was poured into water and extracted with ethyl  
10 acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give methyl 3-[[tert-butoxycarbonyl]amino]methyl]-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-  
15 isoquinolinecarboxylate (1.71 g, 85.9%) as crystals. Melting point 205-207°C.

Elemental analysis for  $C_{27}H_{31}N_2O_5Cl$

Calculated: C, 64.99; H, 6.26; N, 5.61.

20 Found: C, 64.91; H, 6.44; N, 5.34.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.00 (6H, d,  $J=6.6$  Hz), 1.44 (9H, s), 2.14-2.30 (1H, m), 3.87 (3H, s), 4.08 (2H, d,  $J=7.2$  Hz), 4.20 (2H, d,  $J=5.6$  Hz), 4.55 (1H, bs), 7.19-7.25 (2H, m), 7.49-7.56 (2H, m), 7.61 (1H, d,  $J=1.5$  Hz), 8.03 (1H, dd,  
25  $J=1.5, 8.5$  Hz), 8.49 (1H, d,  $J=8.5$  Hz).

(3) To a solution of methyl 3-[[tert-butoxycarbonyl]amino]methyl]-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylate (1.50 g, 3 mmol) in tetrahydrofuran (10 ml)-methanol (10  
30 ml) was added 1N sodium hydroxide (6 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous  
35 magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized

from tetrahydrofuran - isopropyl ether to give 3-  
[[[(tert-butoxycarbonyl)amino]methyl]-4-(4-chlorophenyl)-  
2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic  
acid (1.41 g, 97.2%) as crystals.

5 Melting point 226-227°C.

Elemental analysis for  $C_{26}H_{29}N_2O_5Cl$

Calculated: C, 64.39; H, 6.03; N, 5.78.

Found: C, 64.50; H, 6.36; N, 5.37.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.98 (6H, d,  $J=6.6$  Hz), 1.49 (9H, s),  
10 2.10-2.26 (1H, m), 4.04 (2H, d,  $J=6.6$  Hz), 4.14 (2H, s),  
5.65 (1H, bs), 7.29 (2H, d,  $J=8.2$  Hz), 7.44 (1H, s),  
7.52 (2H, d,  $J=8.2$  Hz), 7.83 (1H, d,  $J=8.0$  Hz), 8.32 (1H,  
d,  $J=8.0$  Hz).

(4) A solution of 3-[[[(tert-  
15 butoxycarbonyl)amino]methyl]-4-(4-chlorophenyl)-2-  
isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid  
(1.21 g, 2.5 mmol), 1-ethyl-3-(3-  
dimethylaminopropyl)carbodiimide hydrochloride (0.96 g,  
5 mmol) and 1-hydroxybenzotriazole ammonium salt (0.76 g,  
20 5 mmol) in N,N-dimethylformamide (10 ml) was stirred at  
room temperature for 2 h. The reaction mixture was  
poured into water and extracted with ethyl acetate. The  
extract was washed with brine, dried over anhydrous  
magnesium sulfate and concentrated under reduced  
25 pressure. The obtained crystals were recrystallized  
from ethyl acetate - diisopropyl ether to give 3-  
[[[(tert-butoxycarbonyl)amino]methyl]-4-(4-chlorophenyl)-  
2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide  
(1.02 g, 85.0%) as crystals.

30 Melting point 144-146°C.

Elemental analysis for  $C_{26}H_{30}N_3O_4Cl \cdot 0.25H_2O$

Calculated: C, 63.93; H, 6.29; N, 8.60.

Found: C, 64.06; H, 6.06; N, 8.53.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (6H, d,  $J=6.6$  Hz), 1.45 (9H, s),  
35 2.14-2.26 (1H, m), 4.06 (2H, d,  $J=6.9$  Hz), 4.18 (2H, d,  
 $J=4.5$  Hz), 4.92 (1H, bs), 5.89 (1H, bs), 6.22 (1H, bs),

7.24 (2H, d, J=8.4 Hz), 7.35 (1H, d, J=1.2 Hz), 7.50 (2H, d, J=8.4 Hz), 7.66 (1H, dd, J=1.2, 8.4 Hz), 8.35 (1H, d, J=8.4 Hz).

(5) 3-[[ (Tert-butoxycarbonyl)amino]methyl]-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide (0.48 g, 1 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol-diethyl ether to give 3-(aminomethyl)-4-(4-chlorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carboxamide hydrochloride (0.41 g, 97.6%) as crystals.

15 Melting point 260-261°C.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.92 (6H, d, J=6.6 Hz), 1.99-2.17 (1H, m), 3.85 (2H, s), 4.08 (2H, d, J=7.0 Hz), 7.44 (2H, d, J=8.0 Hz), 7.45 (1H, d, J=1.5 Hz), 7.60 (1H, bs), 7.64 (2H, d, J=8.0 Hz), 8.01 (1H, d, J=1.5, 8.4 Hz), 8.19 (1H, bs), 8.38 (1H, d, J=8.4 Hz), 8.56 (3H, bs).

#### Example 187

3-(Aminomethyl)-4-(4-chlorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carbonitrile hydrochloride.

(1) A solution of 3-[[ (tert-butoxycarbonyl)amino]methyl]-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide (Example 186 (4)) (0.48 g, 1 mmol) and cyanuric chloride (0.55 g, 3 mmol) in N,N-dimethylformamide (10 mmol) was stirred at 0°C for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [4-(4-chlorophenyl)-6-cyano-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.37 g, 80.4%) as crystals.

Melting point 234-235°C.

Elemental analysis  $C_{26}H_{28}N_3O_3Cl$

Calculated: C, 67.02; H, 6.06; N, 9.02.

Found: C, 67.10; H, 6.09; N, 9.07.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.00 (6H, d, J=6.6 Hz), 1.43 (9H, s), 2.16-2.30 (1H, m), 4.08 (2H, d, J=7.4 Hz), 4.22 (2H, d, J=5.8 Hz), 4.44 (1H, bs), 7.16-7.23 (2H, m), 7.26 (1H, d, J=1.6 Hz), 7.51-7.58 (2H, m), 7.65 (1H, dd, J=1.6, 8.6 Hz), 8.55 (1H, d, J=8.6 Hz).

(2) Tert-butyl [4-(4-chlorophenyl)-6-cyano-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.28 g, 0.6 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol - diethyl ether to give 3-(aminomethyl)-4-(4-chlorophenyl)-2-isobutyl-1(2H)-isoquinolinone-6-carbonitrile hydrochloride (0.23 g, 95.8%) as crystals.

Melting point 280-281°C.

Elemental analysis for  $C_{21}H_{21}N_3OCl$

Calculated: C, 62.69; H, 5.26; N, 10.44.

Found: C, 62.34; H, 5.31; N, 10.45.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.93 (6H, d, J=6.6 Hz), 1.99-2.19 (1H, m), 3.87 (2H, s), 4.10 (2H, d, J=7.4 Hz), 7.32 (1H, d, J=1.4 Hz), 7.43-7.49 (2H, m), 7.64-7.68 (2H, m), 7.97 (1H, dd, J=1.4, 8.4 Hz), 8.47 (1H, d, J=8.4 Hz), 8.67 (3H, bs).

#### Example 188

(E)-3-[3-(Aminomethyl)-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide hydrochloride

(1) A suspension of tert-butyl [4-(4-chlorophenyl)-2-isobutyl-1-oxo-6-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinyl]methylcarbamate (Example 186 (1)) (2.06 g, 3.5 mmol), butyl acrylate (0.76 ml, 5.3

- mmol), sodium hydrogencarbonate (0.45 g, 5.3 mmol), tetrabutylammonium chloride (0.11 g, 0.4 mmol) and palladium acetate (0.09 g, 0.4 mmol) in N,N-dimethylformamide (20 ml) was stirred with heating at 100°C under an argon atmosphere for 48 h. The reaction mixture was poured into water and extracted with ethyl acetate. After washing the extract with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give butyl (E)-3-[3-[[tert-butoxycarbonyl]amino]methyl]-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenate (0.48 g, 23.8%) as crystals. Melting point 149-150°C.
- Elemental analysis for  $C_{32}H_{39}N_2O_5Cl \cdot 0.25H_2O$ .  
Calculated: C, 67.24; H, 6.97; N, 4.90.  
Found: C, 67.22; H, 7.01; N, 4.93.
- $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.95 (3H, t,  $J=7.4$  Hz), 1.00 (6H, d,  $J=6.4$  Hz), 1.32-1.50 (11H, m), 1.59-1.71 (2H, m), 2.14-2.30 (1H, m), 4.07 (2H, d,  $J=7.6$  Hz), 4.16-4.22 (4H, m), 4.43 (1H, bs), 6.40 (1H, d,  $J=16.2$  Hz), 6.98 (1H, d,  $J=1.4$  Hz), 7.20 (2H, d,  $J=8.4$  Hz), 7.52 (2H, d,  $J=8.4$  Hz), 7.55 (1H, d,  $J=16.2$  Hz), 7.63 (1H, dd,  $J=1.4, 8.4$  Hz), 8.45 (1H, d,  $J=8.4$  Hz).
- (2) To a solution of butyl (E)-3-[3-[[tert-butoxycarbonyl]amino]methyl]-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenate (0.41 g, 0.7 mmol) in tetrahydrofuran (10 ml)-methanol (10 ml) was added 1N sodium hydroxide (2 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give (E)-3-[3-

[[ (tert-butoxycarbonyl)amino]methyl]-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenic acid (0.34 g, 91.9%) as crystals.

Melting point 147-149°C.

5 Elemental analysis for  $C_{28}H_{31}N_2O_5Cl \cdot 0.25H_2O$

Calculated: C, 65.24; H, 6.16; N, 5.43.

Found: C, 65.18; H, 6.15; N, 5.31.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (6H, d, J=6.4 Hz), 1.48 (9H, s),  
2.08-2.28 (1H, m), 4.05 (2H, d, J=5.8 Hz), 4.14 (2H, s),  
10 5.46 (1H, bs), 6.32 (1H, d, J=15.8 Hz), 6.82 (1H, s),  
7.26-7.31 (2H, m), 7.42-7.56 (4H, m), 8.28 (1H, d, J=7.8 Hz).

(3) A solution of (E)-3-[3-[[ (tert-butoxycarbonyl)amino]methyl]-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenic  
15 acid (0.20 g, 0.4 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.15 g, 0.8 mmol) and 1-hydroxybenzotriazole ammonium salt (0.12 g, 0.8 mmol) in N,N-dimethylformamide (10 ml) was  
20 stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was crystallized from  
25 ethyl acetate, - n-hexane to give (E)-3-[3-[[ (tert-butoxycarbonyl)amino]methyl]-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide (0.18 g, 90.0%) as crystals.

Melting point 152-154°C.

30 Elemental analysis for  $C_{28}H_{32}N_3O_4Cl \cdot 0.25H_2O$

Calculated: C, 65.36; H, 6.37; N, 8.17.

Found: C, 65.30; H, 6.27; N, 7.99.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (6H, d, J=6.6 Hz), 1.45 (9H, s),  
2.12-2.28 (1H, m), 4.05 (2H, d, J=7.2 Hz), 4.18 (2H, d,  
35 J=4.6 Hz), 4.95 (1H, bs), 5.72 (1H, bs), 5.85 (1H, bs),  
6.37 (1H, d, J=15.8 Hz), 6.91 (1H, d, J=1.2 Hz), 7.24

(2H, d, J=8.8 Hz), 7.41-7.54 (4H, m), 8.28 (1H, d, J=8.4 Hz).

(4) A solution of (E)-3-[3-[[[tert-butoxycarbonyl)amino]methyl]-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide (0.15 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 1 h.

The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate to give (E)-3-[3-(aminomethyl)-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenamide hydrochloride (0.12 g, 92.3%) as crystals.

Melting point 261-263°C.

Elemental analysis for  $C_{23}H_{25}N_3O_2Cl_2 \cdot 0.75H_2O$

Calculated: C, 60.07; H, 5.81; N, 9.14.

Found: C, 59.78; H, 6.14; N, 8.75.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.92 (6H, d, J=6.6 Hz), 1.91-2.21 (1H, m), 3.85 (2H, s), 4.06 (2H, d, J=7.4 Hz), 6.58 (1H, d, J=15.8 Hz), 7.02 (1H, s), 7.19 (1H, bs), 7.34-7.47 (3H, m), 7.62-7.67 (3H, m), 7.79 (1H, d, J=8.0 Hz), 8.35 (1H, d, J=8.0 Hz), 8.60 (3H, bs).

#### Example 189

3-(Aminomethyl)-4-butoxy-2-isobutyl-6-(4-methyl-1,3-thiazol-2-yl)-1(2H)-isoquinolinone dihydrochloride

(1) To a suspension of 3-[[[tert-butoxycarbonyl)amino]methyl]-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxamide (0.44 g, 1 mmol) in toluene (20 ml) was added Lawesson's reagent (0.24 g, 0.6 mmol), and the mixture was refluxed under heating for 1 h. The reaction mixture was purified by silica gel column chromatography to give tert-butyl [6-(aminothiocarbonyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.18 g, 39.1%) as crystals.



Melting point 189-190°C.

Elemental analysis for  $C_{24}H_{35}N_3O_4S$

Calculated: C, 62.44; H, 7.64; N, 9.10.

Found: C, 62.38; H, 7.51; N, 8.89.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.93 (6H, d, J=6.6 Hz), 1.02 (3H, t, J=7.3 Hz), 1.50-1.64 (11H, m), 1.80-1.93 (2H, m), 2.04-2.18 (1H, m), 3.83 (2H, t, J=6.8 Hz), 3.96 (2H, d, J=7.4 Hz), 4.48 (2H, d, J=5.6 Hz), 5.37 (1H, bs), 7.67 (1H, d, J=8.3 Hz), 7.83-7.90 (2H, m), 8.05 (1H, d, J=8.3 Hz),

8.31 (1H, bs).

(2) A suspension of tert-butyl [6-(aminothiocarbonyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]-methylcarbamate (0.46 g, 1 mmol), bromoacetone (0.20 g, 1.5 mmol) and sodium acetate (0.12 g, 1.5 mmol) in ethanol (10 ml) was refluxed under heating for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl[4-butoxy-2-isobutyl-6-(4-methyl-1,3-thiazol-2-yl)-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.36 g, 73.5%) as an amorphous.

Elemental analysis for  $C_{27}H_{37}N_3O_4S$

Calculated: C, 64.90; H, 7.46; N, 8.41.

Found: C, 64.63; H, 7.58; N, 8.26.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.98 (6H, d, J=7.0 Hz), 1.07 (3H, t, J=7.3 Hz), 1.47 (9H, s), 1.56-1.75 (2H, m), 1.84-1.98 (2H, m), 2.12-2.26 (1H, m), 2.55 (3H, d, J=0.8 Hz), 3.92 (2H, t, J=6.4 Hz), 4.00 (2H, d, J=7.4 Hz), 4.54 (2H, d, J=5.8 Hz), 4.78 (1H, bs), 6.98 (1H, q, J=0.8 Hz), 8.08 (1H, dd, J=1.8, 8.4 Hz), 8.22 (1H, d, J=1.8 Hz), 8.46 (1H, d, J=8.4 Hz).

(3) Tert-butyl [4-butoxy-2-isobutyl-6-(4-methyl-1,3-thiazol-2-yl)-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.30 g, 0.6 mmol) was

dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol - diisopropyl ether to give 3-(aminomethyl)-4-butoxy-2-isobutyl-6-(4-methyl-1,3-thiazol-2-yl)-1(2H)-isoquinolinone dihydrochloride (0.27 g, 96.4%) as crystals.

10 Melting point 201-202°C.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.90 (6H, d, J=6.6 Hz), 1.04 (3H, t, J=7.1 Hz), 1.56-1.74 (2H, m), 1.82-2.12 (3H, m), 2.48 (3H, d, J=0.6 Hz), 3.98-4.02 (4H, m), 4.21 (2H, d, J=5.2 Hz), 7.51 (1H, q, J=0.6 Hz), 8.13 (1H, dd, J=1.6, 8.4 Hz), 8.25 (1H, d, J=1.6 Hz), 8.37 (1H, d, J=8.4 Hz), 8.76 (3H, bs).

#### Example 190

Ethyl 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylate hydrochloride

20 (1) Tert-butyl [6-(aminothiocarbonyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (Example 189 (1)) (1.38 g, 3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (10 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was suspended in tetrahydrofuran (20 ml). To the obtained mixture were added triethylamine (0.84 ml, 6 mmol) and 9-fluorenylmethylchloroformate (1.16 g, 4.5 mmol) and the mixture was stirred at 0°C for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 9H-fluoren-9-

ylmethyl [6-(aminocarbothioyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (1.52 g, 86.9%) as an amorphous.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.94-1.00 (9H, m), 1.47-1.59 (2H, m), 1.74-1.83 (2H, m), 2.07-2.18 (1H, m), 3.77 (2H, t, J=6.3 Hz), 3.98 (2H, d, J=6.6 Hz), 4.25 (1H, t, J=6.6 Hz), 4.51-4.53 (4H, m), 5.79 (1H, bs), 7.26-7.41 (4H, m), 7.63-7.66 (3H, m), 7.75 (2H, d, J=7.2 Hz), 7.86 (1H, bs), 7.93 (1H, s), 8.00 (1H, bs), 8.12 (1H, d, J=8.1 Hz).

- 10 (2) A solution of 9H-fluoren-9-ylmethyl [6-(aminocarbothioyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.29 g, 0.5 mmol) and ethyl bromopyruvate (0.19 g, 1 mmol) in ethanol (10 ml) was refluxed under heating for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was crystallized from ethyl acetate - diisopropyl ether to give ethyl 2-[4-butoxy-3-[[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]methyl]-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylate (0.30 g, 90.9%) as crystals.

Melting point 203-203.5°C.

- 25 Elemental analysis for C<sub>39</sub>H<sub>41</sub>N<sub>3</sub>O<sub>6</sub>S

Calculated: C, 68.90; H, 6.08; N, 6.18.

Found: C, 68.64; H, 6.10; N, 6.06.

- <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.97 (6H, d, J=6.6 Hz), 1.07 (3H, t, J=7.1 Hz), 1.45 (3H, t, J=7.0 Hz), 1.56-1.75 (2H, m), 1.81-1.98 (2H, m), 2.06-2.24 (1H, m), 3.94 (2H, t, J=6.4 Hz), 4.05 (2H, d, J=7.0 Hz), 4.22 (1H, t, J=6.6 Hz), 4.47 (2H, q, J=7.0 Hz), 4.49 (2H, d, J=6.6 Hz), 4.59 (2H, d, J=5.4 Hz), 5.23 (1H, bs), 7.29-7.43 (4H, m), 7.59 (2H, d, J=7.3 Hz), 8.14 (1H, dd, J=1.6, 8.4 Hz), 8.24-8.26 (2H, m), 8.47 (1H, d, J=8.4 Hz).

- 35 (3) To a solution of ethyl 2-[4-butoxy-3-[[[(9H-fluoren-

9-ylmethoxy)carbonylamino]methyl]-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylate (1.70 g, 2.5 mmol) in N,N-dimethylformamide (25 ml)-tetrahydrofuran(25 ml) was added pyrrolidine (2 ml), and  
5 the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in  
10 tetrahydrofuran (20 ml) and di-t-butyl dicarbonate (0.89 ml, 4 mmol) was added thereto. The obtained mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over  
15 anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give ethyl 2-[4-butoxy-3-[[ (tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylate  
20 (1.21 g, 87.1%) as crystals.

Melting point 172-172.5°C.

Elemental analysis for  $C_{29}H_{39}N_3O_6S$

Calculated: C, 62.45; H, 7.05; N, 7.53.

Found: C, 62.50; H, 7.04; N, 7.53.

25  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.98 (6H, d,  $J=6.6$  Hz), 1.07 (3H, t,  $J=7.3$  Hz), 1.45 (3H, t,  $J=7.2$  Hz), 1.47 (9H, s), 1.62-1.78 (2H, m), 1.85-1.99 (2H, m), 2.12-2.26 (1H, m), 3.93 (2H, t,  $J=6.4$  Hz), 4.01 (2H, d,  $J=7.2$  Hz), 4.47 (2H, q,  $J=7.2$  Hz), 4.54 (2H, d,  $J=6.6$  Hz), 4.77 (1H, bs), 8.16  
30 (1H, dd,  $J=1.8, 8.4$  Hz), 8.25 (1H, s), 8.28 (1H, d,  $J=1.8$  Hz), 8.49 (1H, d,  $J=8.4$  Hz).

(4) Ethyl 2-[4-butoxy-3-[[ (tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylate  
35 (0.17 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml), and the

mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from ethyl acetate - diisopropyl ether to give ethyl 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylate hydrochloride (0.13 g, 92.9%) as crystals.

Melting point 224-226°C.

Elemental analysis for  $C_{24}H_{32}N_3O_4ClS \cdot H_2O$

10 Calculated: C, 56.29; H, 6.69; N, 8.21.

Found: C, 56.00; H, 6.43; N, 7.99.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.91 (6H, d,  $J=6.6$  Hz), 1.05 (3H, t,  $J=7.1$  Hz), 1.36 (3H, t,  $J=7.2$  Hz), 1.57-1.76 (2H, m), 1.83-2.16 (3H, m), 3.98-4.06 (4H, m), 4.22 (2H, d,  $J=4.6$  Hz), 4.37 (2H, q,  $J=7.2$  Hz), 8.20 (1H, dd,  $J=1.4, 8.4$  Hz), 8.31 (1H, d,  $J=1.4$  Hz), 8.42 (1H, d,  $J=8.4$  Hz), 8.66 (3H, bs), 8.73 (1H, s).

#### Example 191

2-[3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylic acid hydrochloride

(1) To a solution of ethyl 2-[4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylate (1.12 g, 2 mmol) in tetrahydrofuran (10 ml)- ethanol (5 ml) was added 1N sodium hydroxide (4 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give 2-[4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylic acid (0.97 g, 92.4%) as crystals.

Melting point 195-196°C.

Elemental analysis for  $C_{27}H_{35}N_3O_6S$

Calculated: C, 61.23; H, 6.66; N, 7.93.

Found: C, 61.10; H, 6.71; N, 7.65.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.98 (6H, d, J=7.0 Hz), 1.08 (3H, t, J=7.4 Hz), 1.48 (9H, s), 1.57-1.76 (2H, m), 1.85-1.99 (2H, m), 2.13-2.26 (1H, m), 3.93 (2H, t, J=6.2 Hz), 4.02 (2H, d, J=7.2 Hz), 4.56 (2H, d, J=5.6 Hz), 4.92 (1H, bs), 8.11 (1H, dd, J=1.8, 8.4 Hz), 8.24 (1H, d, J=1.8 Hz), 8.36 (1H, s), 8.49 (1H, d, J=8.4 Hz).

(2) 2-[4-Butoxy-3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylic acid (0.16 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was crystallized from ethyl acetate to give 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylic acid hydrochloride (0.13 g, 92.9%) as crystals.

Melting point 244-246°C.

Elemental analysis for  $C_{22}H_{28}N_3O_4ClS \cdot 0.5H_2O$

Calculated: C, 55.63; H, 6.15; N, 8.85.

Found: C, 55.45; H, 6.49; N, 8.51.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.91 (6H, d, J=6.6 Hz), 1.04 (3H, t, J=7.2 Hz), 1.60-1.72 (2H, m), 1.84-1.93 (2H, m), 2.00-2.10 (1H, m), 3.99-4.02 (4H, m), 4.22 (2H, s), 8.21 (1H, dd, J=1.5, 8.4 Hz), 8.30 (1H, d, J=1.5 Hz), 8.42 (1H, d, J=8.4 Hz), 8.63 (3H, bs), 8.66 (1H, s).

#### Example 192

2-[3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxamide hydrochloride

(1) A solution of 2-[4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-1,2-

dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylic acid (0.79 g, 1.5 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.58 g, 3 mmol) and 1-hydroxybenzotriazole ammonium salt (0.46 g, 3 mmol) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran-diisopropyl ether to give tert-butyl [6-[4-(aminocarbonyl)-1,3-thiazol-2-yl]-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.74 g, 93.7%) as crystals.

Melting point 195-196°C.

Elemental analysis for  $C_{27}H_{36}N_4O_4S \cdot 0.5H_2O$

Calculated: C, 60.31; H, 6.94; N, 10.42.

Found: C, 60.62; H, 7.08; N, 10.19.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.98 (6H, d,  $J=6.8$  Hz), 1.07 (3H, t,  $J=7.2$  Hz), 1.48 (9H, s), 1.57-1.98 (4H, m), 2.11-2.28 (1H, m), 3.92 (2H, t,  $J=6.2$  Hz), 4.02 (2H, d,  $J=7.4$  Hz), 4.55 (2H, d,  $J=5.4$  Hz), 4.91 (1H, bs), 5.89 (1H, bs), 7.29 (1H, bs), 8.04-8.09 (1H, m), 8.24-8.25 (1H, m), 8.46-8.51 (2H, m).

(2) Tert-butyl [6-[4-(aminocarbonyl)-1,3-thiazol-2-yl]-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.32 g, 0.6 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was crystallized from ethyl acetate to give 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxamide hydrochloride (0.26 g, 92.6%) as crystals. Melting point 274-276°C.

Elemental analysis for  $C_{22}H_{29}N_4O_3ClS \cdot 0.5H_2O$

Calculated: C, 55.74; H, 6.38; N, 11.82.

Found: C, 56.13; H, 6.33; N, 11.86.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.91 (6H, d,  $J=6.6$  Hz), 1.04 (3H, t,  $J=7.1$  Hz), 1.56-1.75 (2H, m), 1.84-2.18 (3H, m), 3.99-4.05 (4H, m), 4.22 (2H, d,  $J=4.4$  Hz), 8.28 (1H, d,  $J=1.6$  Hz), 8.30 (1H, dd,  $J=1.6, 9.2$  Hz), 8.41 (1H, d,  $J=9.2$  Hz), 8.46 (1H, s), 8.71 (3H, bs).

#### Example 193

2-[3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carbonitrile hydrochloride

(1) A solution of tert-butyl[6-[4-(aminocarbonyl)-1,3-thiazol-2-yl]-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.32 g, 0.6 mmol) and cyanuric chloride (0.33 g, 1.8 mmol) in N,N-dimethylformamide (10 mmol) was stirred at 0°C for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [4-butoxy-6-(4-cyano-1,3-thiazol-2-yl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.28 g, 93.3%) as crystals.

Melting point 160-161°C.

Elemental analysis for  $C_{27}H_{34}N_4O_4S$

Calculated: C, 63.51; H, 6.71; N, 10.97.

Found: C, 63.47; H, 6.69; N, 10.99.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.98 (6H, d,  $J=6.9$  Hz), 1.08 (3H, t,  $J=7.5$  Hz), 1.48 (9H, s), 1.60-1.72 (2H, m), 1.87-1.97 (2H, m), 2.12-2.24 (1H, m), 3.92 (2H, t,  $J=6.4$  Hz), 4.01 (2H, d,  $J=7.5$  Hz), 4.55 (2H, d,  $J=5.4$  Hz), 4.86 (1H, bs), 8.01 (1H, dd,  $J=1.8, 8.2$  Hz), 8.08 (1H, s), 8.29 (1H, d,  $J=1.8$  Hz), 8.49 (1H, d,  $J=8.2$  Hz).

(2) Tert-butyl [4-butoxy-6-(4-cyano-1,3-thiazol-2-yl)-2-



isobutyl-1-oxo-1,2-dihydro-3-  
isoquinolinyl)methylcarbamate (0.20 g, 0.4 mmol) was  
dissolved in a solution of 4N hydrogen chloride in ethyl  
acetate (5 ml) and the mixture was stirred at room  
5 temperature for 1 h. The reaction mixture was  
concentrated under reduced pressure, and the residue was  
crystallized from ethyl acetate to give 2-[3-  
(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-  
isoquinolinyl]-1,3-thiazole-4-carbonitrile hydrochloride  
10 (0.17 g, 94.4%) as crystals.

Melting point 167-169°C.

Elemental analysis for  $C_{22}H_{27}N_4O_2ClS \cdot H_2O$

Calculated: C, 56.82; H, 6.29; N, 12.05.

Found: C, 56.92; H, 6.29; N, 11.95.

15  $^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.91 (6H, d,  $J=6.6$  Hz), 1.05 (3H, t,  
 $J=7.2$  Hz), 1.56-1.74 (2H, m), 1.82-2.18 (3H, m), 3.98-  
4.05 (4H, m), 4.22 (2H, s), 8.20 (1H, d,  $J=8.4$  Hz), 8.30  
(1H, s), 8.42 (1H, d,  $J=8.4$  Hz), 8.70 (3H, bs), 9.06 (1H,  
s).

20 **Example 194**

3-(Aminomethyl)-2-isobutyl-6-(4-methyl-1,3-thiazol-2-  
yl)-4-phenyl-1(2H)-isoquinolinone

(1) To a suspension of 3-[[tert-  
butoxycarbonyl)amino]methyl]-2-isobutyl-4-phenyl-1-oxo-  
25 1,2-dihydro-6-isoquinolinecarboxamide (4.05 g, 9 mmol)  
in toluene (50 ml) was added Lawesson's reagent (2.19 g,  
5.4 mmol), and the mixture was refluxed under heating  
for 1 h. The reaction mixture was purified by silica  
gel column chromatography to give tert-butyl [6-  
30 (aminothiocarbonyl)-2-isobutyl-1-oxo-4-phenyl-1,2-  
dihydro-3-isoquinolinyl)methylcarbamate (3.64 g, 86.9%)  
as crystals.

Melting point 228-229°C.

Elemental analysis for  $C_{26}H_{31}N_3O_3S$

35 Calculated: C, 67.07; H, 6.71; N, 9.02.

Found: C, 66.88; H, 6.66; N, 8.85.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.98 (6H, d, J=6.6 Hz), 1.44 (9H, s), 2.12-2.29 (1H, m), 4.07 (2H, d, J=6.9 Hz), 4.20 (2H, d, J=5.1 Hz), 4.79 (1H, bs), 7.23-7.27 (2H, m), 7.33 (1H, d, J=1.6 Hz), 7.37 (1H, bs), 7.46-7.56 (3H, m), 7.74 (1H, bs), 7.76 (1H, dd, J=1.6, 8.6 Hz), 8.29 (1H, d, J=8.6 Hz).

(2) Tert-butyl [6-(aminothiocarbonyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (3.26 g, 7 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (20 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was suspended in tetrahydrofuran (20 ml). To the obtained mixture were added triethylamine (2.0 ml, 14 mmol) and 9-fluorenylmethyl chloroformate (2.72 g, 10.5 mmol) and the mixture was stirred with heating at 0°C for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 9H-fluoren-9-ylmethyl [6-(aminocarbothioyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (3.21 g, 78.1%) as an amorphous.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.97 (6H, d, J=6.6 Hz), 2.07-2.24 (1H, m), 4.08 (2H, d, J=7.4 Hz), 4.19 (1H, t, J=6.8 Hz), 4.25 (2H, d, J=2.6 Hz), 4.41 (2H, d, J=6.8 Hz), 5.35 (1H, bs), 7.21-7.60 (13H, m), 7.72-7.76 (3H, m), 8.26 (1H, d, J=8.6 Hz).

(3) A suspension of 9H-fluoren-9-ylmethyl [6-(aminocarbothioyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.47 g, 0.8 mmol) and bromoacetone (0.22 g, 1.6 mmol) in ethanol (10 ml) was refluxed under heating for 1 h. The reaction mixture was poured into water and extracted with ethyl

acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 9H-fluoren-9-ylmethyl [2-isobutyl-6-(4-methyl-1,3-thiazol-2-yl)-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.41 g, 82.0%) as an amorphous.

Elemental analysis for  $C_{39}H_{35}N_3O_3S \cdot 0.25H_2O$

Calculated: C, 74.32; H, 5.68; N, 6.67.

10 Found: C, 74.36; H, 5.44; N, 6.62.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.00 (6H, d,  $J=6.8$  Hz), 2.12-2.29 (1H, m), 2.44 (3H, d,  $J=0.8$  Hz), 4.06 (2H, d,  $J=7.2$  Hz), 4.19 (2H, t,  $J=6.6$  Hz), 4.27 (2H, d,  $J=5.0$  Hz), 4.44 (2H, d,  $J=6.6$  Hz), 4.86 (1H, bs), 6.86 (1H, q,  $J=0.8$  Hz), 7.26-7.44 (7H, m), 7.52-7.57 (5H, m), 7.75 (2H, d,  $J=7.0$  Hz), 8.02 (1H, dd,  $J=1.8, 8.4$  Hz), 8.50 (1H, d,  $J=8.4$  Hz).

(4) To a solution of 9H-fluoren-9-ylmethyl [2-isobutyl-6-(4-methyl-1,3-thiazol-2-yl)-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.38 g, 0.6

20 mmol) in N,N-dimethylformamide (10 ml) was added pyrrolidine (0.5 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The residue was purified by silica gel column chromatography to give 3-(aminomethyl)-2-isobutyl-6-(4-methyl-1,3-thiazol-2-yl)-4-phenyl-1(2H)-isoquinolinone (0.13 g, 54.2%) as crystals.

Melting point 162-163°C.

Elemental analysis for  $C_{24}H_{24}N_3OS \cdot 0.25H_2O$

30 Calculated: C, 70.64; H, 6.30; N, 10.30.

Found: C, 70.96; H, 6.38; N, 10.16.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.02 (6H, d,  $J=7.0$  Hz), 1.35 (2H, bs), 2.13-2.35 (1H, m), 2.45 (3H, d,  $J=1.2$  Hz), 3.69 (2H, s), 4.23 (2H, d,  $J=7.2$  Hz), 6.85 (1H, q,  $J=1.2$  Hz), 7.30-7.35 (2H, m), 7.43 (1H, d,  $J=1.4$  Hz), 7.48-7.59 (3H, m), 8.03 (1H, dd,  $J=1.4, 8.4$  Hz), 8.52 (1H, d,  $J=8.4$  Hz).

**Example 195**

Ethyl 2-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylate hydrochloride

- 5 (1) A solution of 9H-fluoren-9-ylmethyl [6-(aminocarbothioyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (Example 194(2)) (2.35 g, 4 mmol) and ethyl bromopyruvate (1.56 g, 8 mmol) in ethanol (20 ml) was refluxed under heating for  
10 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give  
15 ethyl 2-[3-[[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylate (1.92 g, 70.3%) as crystals.

Melting point 151-152°C.

- 20 Elemental analysis for  $C_{41}H_{37}N_3O_5S$

Calculated: C, 72.01; H, 5.45; N, 6.14.

Found: C, 71.79; H, 5.59; N, 6.02.

- $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.00 (6H, d,  $J=6.6$  Hz), 1.41 (3H, t,  $J=7.2$  Hz), 2.16-2.27 (1H, m), 4.07 (2H, d,  $J=5.7$  Hz),  
25 4.19 (1H, t,  $J=6.6$  Hz), 4.28 (2H, d,  $J=5.4$  Hz), 4.38-4.45 (4H, m), 4.86 (1H, bs), 7.28-7.45 (7H, m), 7.75 (2H, d,  $J=7.1$  Hz), 8.11 (1H, s), 8.13 (1H, dd,  $J=1.8, 8.4$  Hz), 8.53 (1H, d,  $J=8.4$  Hz).

- (2) To a solution of ethyl 2-[3-[[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylate (1.84 g, 2.7 mmol) in N,N-dimethylformamide  
30 (20 ml) was added pyrrolidine (1 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl  
35 acetate. The extract was washed with brine, dried over

anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 ml) and di-*t*-butyl dicarbonate (0.9 ml, 4 mmol) was added thereto. The obtained mixture was  
5 stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica  
10 gel column chromatography to give ethyl 2-[3-[[*(tert*-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylate (1.41 g, 93.4%) as crystals.

Melting point 170.5-171°C.

15 Elemental analysis for  $C_{29}H_{39}N_3O_6S$

Calculated: C, 62.45; H, 7.05; N, 7.53.

Found: C, 62.50; H, 7.04; N, 7.53.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.02 (6H, d,  $J=6.6$  Hz), 1.41 (3H, t,  $J=7.0$  Hz), 1.44 (9H, s), 2.11-2.38 (1H, m), 4.19 (2H, d,  $J=7.2$  Hz), 4.23 (2H, d,  $J=5.4$  Hz), 4.42 (2H, q,  $J=7.0$  Hz),  
20 4.60 (1H, bs), 7.28-7.33 (2H, m), 7.45 (1H, d,  $J=1.8$  Hz), 7.51-7.61 (3H, m), 8.11 (1H, s), 8.13 (1H, dd,  $J=1.8$ , 8.4 Hz), 8.52 (1H, d,  $J=8.4$  Hz).

(3) Ethyl 2-[3-[[*(tert*-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-  
25 1,3-thiazole-4-carboxylate (0.17 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was  
30 concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol - diisopropyl ether to give ethyl 2-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylate hydrochloride (0.13 g, 92.9%)  
35 as crystals.

Melting point 265-267°C.

Elemental analysis for  $C_{26}H_{28}N_3O_3ClS \cdot 0.5H_2O$

Calculated: C, 61.59; H, 5.76; N, 8.29.

Found: C, 61.75; H, 5.77; N, 8.40.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.94 (6H, d,  $J=6.6$  Hz), 1.30 (3H, t,  $J=7.2$  Hz), 3.91 (2H, s), 4.11 (2H, d,  $J=7.2$  Hz), 4.30 (2H, q,  $J=7.2$  Hz), 7.46-7.50 (3H, m), 7.60-7.72 (3H, m), 8.15 (1H, dd,  $J=1.4, 8.4$  Hz), 8.48 (1H, d,  $J=8.4$  Hz), 8.59 (1H, s), 8.40 (3H, bs).

#### Example 196

2-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylic acid hydrochloride

(1) To a solution of ethyl 2-[3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylate (1.12 g, 2 mmol) in tetrahydrofuran (10 ml)-ethanol (10 ml) was added 1N sodium hydroxide (4 ml) and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate - diisopropyl ether to give 2-[3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylic acid (1.02 g, 96.2%) as crystals.

Melting point 213-214°C.

Elemental analysis for  $C_{29}H_{31}N_3O_5S$

Calculated: C, 65.27; H, 5.86; N, 7.87.

Found: C, 65.01; H, 5.65; N, 7.65.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.02 (6H, d,  $J=6.6$  Hz), 1.45 (9H, s), 2.18-2.34 (1H, m), 4.10 (2H, d,  $J=7.4$  Hz), 4.23 (2H, d,  $J=5.2$  Hz), 4.88 (1H, bs), 6.40 (1H, bs), 7.33-7.41 (3H, m), 7.47-7.58 (3H, m), 8.03 (1H, dd,  $J=1.8, 8.4$  Hz), 8.21 (1H, s), 8.49 (1H, d,  $J=8.4$  Hz).

(2) 2-[3-[[[Tert-butoxycarbonyl]amino]methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylic acid (0.16 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was crystallized from ethyl acetate to give 2-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylic acid hydrochloride (0.13 g, 92.9%) as crystals. Melting point 281-283°C.

Elemental analysis for  $C_{24}H_{24}N_3O_3ClS \cdot H_2O$ .

Calculated: C, 59.07; H, 5.37; N, 8.61.

Found: C, 59.32; H, 5.42; N, 8.57.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.94 (6H, d,  $J=6.6$  Hz), 2.01-2.21 (1H, m), 3.90 (2H, s), 4.10 (2H, d,  $J=7.8$  Hz), 7.45-7.51 (3H, m), 7.56-7.64 (3H, m), 8.41 (1H, dd,  $J=1.7, 8.4$  Hz), 8.48 (1H, d,  $J=8.4$  Hz), 8.53 (1H, s), 8.57 (3H, bs).

#### Example 197

2-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxamide hydrochloride

(1) A solution of 2-[3-[[[tert-butoxycarbonyl]amino]methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxylic acid (0.80 g, 1.5 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.58 g, 3 mmol) and 1-hydroxybenzotriazole ammonium salt (0.46 g, 3 mmol) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran - diisopropyl ether to give tert-

butyl[6-[4-(aminocarbonyl)-1,3-thiazol-2-yl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.75 g, 93.8%) as crystals.

5 Melting point 248-249°C.

Elemental analysis for  $C_{29}H_{32}N_4O_4S \cdot 0.25H_2O$

Calculated: C, 64.84; H, 6.10; N, 10.43.

Found: C, 64.98; H, 6.21; N, 10.23.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.02 (6H, d, J=6.8 Hz), 1.44 (9H, s),  
10 2.19-2.34 (1H, m), 4.10 (2H, d, J=7.4 Hz), 4.24 (2H, d, J=5.4 Hz), 4.65 (1H, bs), 5.84 (1H, bs), 7.29-7.34 (2H, m), 7.44 (1H, d, J=1.8 Hz), 7.51-7.61 (3H, m), 8.00 (1H, dd, J=1.8, 8.4 Hz), 8.11 (1H, s), 8.52 (1H, d, J=8.4 Hz).

(2) Tert-butyl [6-[4-(aminocarbonyl)-1,3-thiazol-2-yl]-  
15 2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]-methylcarbamate (0.32 g, 0.6 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced  
20 pressure and the residue was crystallized from ethyl acetate to give 2-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carboxamide hydrochloride (0.27 g, 96.4%) as crystals. Melting point 235-237°C.

25  $^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.94 (6H, d, J=6.8 Hz), 2.05-2.21 (1H, m), 3.92 (2H, s), 4.10 (2H, d, J=7.8 Hz), 7.39 (1H, d, J=1.6 Hz), 7.45-7.50 (2H, m), 7.60-7.66 (3H, m), 7.70 (1H, bs), 7.79 (1H, bs), 8.28 (1H, d, J=1.6, 8.4 Hz), 8.30 (1H, s), 8.47 (1H, d, J=8.4 Hz), 8.58 (3H, bs).

30 **Example 198**

2-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carbonitrile hydrochloride

(1) A solution of tert-butyl [6-[4-(aminocarbonyl)-1,3-  
35 thiazol-2-yl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.32 g, 0.6 mmol) and



cyanuric chloride (0.33 g, 1.8 mmol) in N,N-dimethylformamide (10 mmol) was stirred at 0°C for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine,  
5 dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [6-(4-cyano-1,3-thiazol-2-yl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.28 g,  
10 90.3%) as crystals.

Melting point 209-211°C.

Elemental analysis for  $C_{29}H_{30}N_4O_3S$

Calculated: C, 67.68; H, 5.88; N, 10.89.

Found: C, 67.72; H, 5.92; N, 10.62.

15  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.02 (6H, d, J=6.8 Hz), 1.44 (9H, s), 2.19-2.38 (1H, m), 4.10 (2H, d, J=7.8 Hz), 4.24 (2H, d, J=5.6 Hz), 4.58 (1H, bs), 7.28-7.32 (2H, m), 7.49 (1H, d, J=1.4 Hz), 7.52-7.63 (3H, m), 7.95 (1H, s), 7.96 (1H, dd, J=1.4, 8.4 Hz), 8.54 (1H, d, J=8.4 Hz).

20 (2) Tert-butyl [6-(4-cyano-1,3-thiazol-2-yl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.21 g, 0.4 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room  
25 temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was crystallized from ethyl acetate to give 2-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazole-4-carbonitrile hydrochloride  
30 (0.17 g, 94.4%) as crystals.

Melting point 274-276°C.

Elemental analysis for  $C_{24}H_{23}N_4OClS \cdot 0.5H_2O$

Calculated: C, 62.67; H, 5.26; N, 12.18.

Found: C, 62.57; H, 5.06; N, 12.08.

35  $^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.94 (6H, d, J=6.6 Hz), 2.01-2.21 (1H, m), 3.89 (2H, m), 4.11 (2H, d, J=7.2 Hz), 7.45-7.51 (3H,

m), 7.61-7.64 (3H, m), 8.14 (1H, dd, J=1.8, 8.4 Hz), 8.48 (1H, d, J=8.4 Hz), 8.62 (3H, bs), 8.95 (1H, s).

**Example 199**

3-(Aminomethyl)-4-butoxy-2-isobutyl-6-(1H-pyrrol-1-yl)-  
1(2H)-isoquinolinone dihydrochloride

(1) A solution of tert-butyl (6-amino-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.41 g, 1 mmol) and 2,5-dimethoxytetrahydrofuran (0.19 ml, 1.5 mmol) in acetic acid (10 ml) was stirred at 80°C for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [4-butoxy-2-isobutyl-1-oxo-6-(1H-pyrrol-1-yl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.31 g, 67.4%) as crystals.

Melting point 164-166°C.

Elemental analysis for  $C_{27}H_{37}N_3O_4$

Calculated: C, 69.35; H, 7.98; N, 8.99.

Found: C, 69.29; H, 8.28; N, 8.87.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.97 (6H, d, J=6.6 Hz), 1.04 (3H, t, J=7.4 Hz), 1.47 (9H, s), 1.51-1.69 (2H, m), 1.81-1.95 (2H, m), 2.04-2.25 (1H, m), 3.89 (2H, t, J=6.5 Hz), 3.99 (2H, d, J=7.8 Hz), 4.53 (2H, d, J=5.6 Hz), 4.80 (1H, bs), 6.41-6.43 (2H, m), 7.21-7.23 (2H, m), 7.50-7.56 (1H, m), 7.62 (1H, d, J=1.8 Hz), 8.43-8.48 (1H, m).

(2) Tert-butyl [4-butoxy-2-isobutyl-1-oxo-6-(1H-pyrrol-1-yl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.23 g, 0.5 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the obtained crystals were recrystallized from methanol - diethyl ether to give 3-(aminomethyl)-4-butoxy-2-

isobutyl-6-(1H-pyrrol-1-yl)-1(2H)-isoquinolinone dihydrochloride (0.19 g, 95.0%) as crystals.

Melting point 156-157°C.

Elemental analysis for  $C_{22}H_{30}N_3O_2Cl \cdot 0.5H_2O$

5 Calculated: C, 63.99; H, 7.57; N, 10.18.

Found: C, 64.23; H, 7.86; N, 10.25.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.90 (6H, d,  $J=6.6$  Hz), 1.00 (3H, t,  $J=7.3$  Hz), 1.55-1.66 (2H, m), 1.81-2.13 (3H, m), 3.96-4.03 (4H, m), 4.19 (2H, bs), 6.39 (2H, t,  $J=2.2$  Hz),  
10 7.55 (2H, t,  $J=2.2$  Hz), 7.70 (1H, d,  $J=2.0$  Hz), 7.89 (1H, dd,  $J=2.0, 8.8$  Hz), 8.33 (1H, d,  $J=8.8$  Hz), 8.72 (3H, bs).

#### Example 200

3-(Aminomethyl)-4-butoxy-2-isobutyl-6-(1H-tetrazol-1-yl)-1(2H)-isoquinolinone hydrochloride

15 (1) To a solution of tert-butyl (6-amino-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.41 g, 1 mmol) in acetic acid (5 ml) was added trimethyl orthoformate (0.33 ml, 3  
20 mmol) and the mixture was stirred at room temperature for 30 min. To the obtained mixture was added sodium azide (0.10 g, 1.5 mmol) and the mixture was stirred at 80°C for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was  
25 washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [4-butoxy-2-isobutyl-1-oxo-6-(1H-tetrazol-1-yl)-1,2-dihydro-3-isoquinolinyl]-  
30 methylcarbamate (0.31 g, 66.0%) as crystals. Melting point 199-200°C.

$^1H$ -NMR(CDCl $_3$ )  $\delta$ : 0.98 (6H, d,  $J=6.6$  Hz), 1.05 (3H, t,  $J=7.3$  Hz), 1.48 (9H, s), 1.54-1.69 (2H, m), 1.83-1.97 (2H, m), 2.12-2.26 (1H, m), 3.91 (2H, t,  $J=6.4$  Hz), 4.03  
35 (2H, d,  $J=7.4$  Hz), 4.56 (2H, d,  $J=5.4$  Hz), 4.80 (1H, bs), 7.78 (1H, dd,  $J=2.2, 8.8$  Hz), 8.09 (1H, d,  $J=2.2$  Hz),

8.62 (1H, d, J=8.8 Hz), 9.15 (1H, s).

(2) Tert-butyl [4-butoxy-2-isobutyl-1-oxo-6-(1H-tetrazol-1-yl)-1,2-dihydro-3-

isoquinolinyl]methylcarbamate (0.24 g, 0.5 mmol) was

5 dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was

concentrated under reduced pressure and the obtained

crystals was crystallized from methanol - diethyl ether

10 to give 3-(aminomethyl)-4-butoxy-2-isobutyl-6-(1H-tetrazol-1-yl)-1(2H)-isoquinolinone hydrochloride (0.19 g, 95.0%) as crystals.

Melting point 177-179°C.

Elemental analysis for  $C_{19}H_{27}N_6O_2Cl \cdot 0.5H_2O$

15 Calculated: C, 54.87; H, 6.79; N, 20.21.

Found: C, 55.08; H, 7.19; N, 20.00.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.91 (6H, d, J=6.6 Hz), 1.01 (3H, t,

J=7.3 Hz), 1.43-1.67 (2H, m), 1.82-2.10 (3H, m), 3.98-

4.04 (4H, m), 4.23 (2H, bs), 8.17 (1H, dd, J=2.0, 8.6

20 Hz), 8.23 (1H, d, J=2.0 Hz), 8.52 (1H, d, J=8.6 Hz),

8.73 (3H, bs), 10.38 (1H, s).

#### Example 201

3-(Aminomethyl)-4-butoxy-2-isobutyl-6-(1H-1,2,3-triazol-1-yl)-1(2H)-isoquinolinone hydrochloride

25 (1) To a solution of tert-butyl (6-amino-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-

isoquinolinyl)methylcarbamate (0.41 g, 1 mmol) in

methanol (10 ml) was added N'-(2,2-dichloroethylidene)-

4-methylbenzenesulfonohydrazide (0.28 g, 1 mmol) and the

30 mixture was stirred at 0°C for 1 h and at room

temperature for 12 h. The reaction mixture was poured

into water and extracted with ethyl acetate. The

extract was washed with brine, dried over anhydrous

magnesium sulfate and concentrated under reduced

35 pressure. The residue was purified by silica gel column chromatography to give tert-butyl [4-butoxy-2-isobutyl-

1-oxo-6-(1H-1,2,3-triazol-1-yl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.21 g, 45.7%) as crystals.

Melting point 190-191°C.

5 Elemental analysis for  $C_{25}H_{35}N_5O_4$

Calculated: C, 63.97; H, 7.51; N, 14.91.

Found: C, 64.95; H, 7.69; N, 14.63.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.98 (6H, d,  $J=6.6$  Hz), 1.04 (3H, t,  $J=7.0$  Hz), 1.48 (9H, s), 1.54-1.69 (2H, m), 1.83-1.97

10 (2H, m), 2.04-2.24 (1H, m), 3.92 (2H, t,  $J=6.6$  Hz), 4.02 (2H, d,  $J=7.8$  Hz), 4.55 (2H, d,  $J=5.6$  Hz), 4.82 (1H, bs), 7.81 (1H, dd,  $J=2.2, 8.8$  Hz), 7.91 (1H, d,  $J=1.3$  Hz), 8.12 (1H, d,  $J=1.3$  Hz), 8.13 (1H, d,  $J=2.2$  Hz), 8.56 (1H, d,  $J=8.8$  Hz).

15 (2) tert-butyl [4-butoxy-2-isobutyl-1-oxo-6-(1H-1,2,3-triazol-1-yl)-1,2-dihydro-3-

isoquinolinyl]methylcarbamate (0.14 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room

20 temperature for 1 h. The reaction mixture was concentrated under reduced pressure to give 3-(aminomethyl)-4-butoxy-2-isobutyl-6-(1H-1,2,3-triazol-1-yl)-1(2H)-isoquinolinone hydrochloride (81 mg, 62.3%) as an amorphous.

25  $^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.91 (6H, d,  $J=6.6$  Hz), 1.01 (3H, t,  $J=7.3$  Hz), 1.49-1.68 (2H, m), 1.82-2.12 (3H, m), 3.89-4.03 (4H, m), 4.22 (2H, d,  $J=4.4$  Hz), 8.09 (1H, d,  $J=1.3$  Hz), 8.18 (1H, dd,  $J=2.0, 8.6$  Hz), 8.24 (1H, d,  $J=2.0$  Hz), 8.48 (1H, d,  $J=8.6$  Hz), 8.75 (3H, bs), 9.11 (1H, d,  $J=1.3$  Hz).

30 Example 202

3-(Aminomethyl)-4-butoxy-2-isobutyl-6-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-1(2H)-isoquinolinone hydrochloride

35 (1) A solution of tert-butyl (4-butoxy-6-cyano-2-isobutyl-1-oxo-1,2-dihydro-3-

isoquinolinyl)methylcarbamate (0.85 g, 2 mmol), sodium carbonate (0.85 g, 8 mmol) and hydroxylamine hydrochloride (0.42 g, 6 mmol) in ethanol (20 ml) was refluxed with stirring for 12 h. The reaction mixture  
5 was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [6-

10 [amino(hydroxyimino)methyl]-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.81 g, 88.0%) as crystals.

Melting point 209-210°C.

Elemental analysis for  $C_{24}H_{36}N_4O_5$

15 Calculated: C, 62.59; H, 7.88; N, 12.16.

Found: C, 62.49; H, 7.93; N, 11.98.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.95 (6H, d,  $J=6.6$  Hz), 1.02 (3H, t,  $J=7.3$  Hz), 1.49-1.66 (11H, m), 1.78-1.91 (2H, m), 2.09-2.24 (1H, m), 3.68-3.84 (2H, m), 3.98 (2H, t,  $J=6.6$  Hz),  
20 4.51 (2H, d,  $J=4.8$  Hz), 5.02 (2H, s), 5.16 (1H, bs), 5.37 (1H, bs), 7.62 (1H, d,  $J=8.3$  Hz), 7.82 (1H, s), 8.25 (1H, d,  $J=8.3$  Hz).

(2) To a solution of tert-butyl [6-[amino(hydroxyimino)methyl]-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.78 g, 1.7  
25 mmol) in ethyl acetate (10 ml)- tetrahydrofuran (10 ml) was added 1,1'-carbonyldiimidazole (0.83 g, 5.1 mmol) and the mixture was stirred at 80°C for 2 h. The reaction mixture was poured into water and extracted  
30 with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was crystallized from ethyl acetate - diisopropyl ether to give tert-butyl [4-butoxy-2-isobutyl-1-oxo-6-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-1,2-dihydro-3-  
35 isoquinolinyl)methylcarbamate (0.54 g, 65.9%) as

crystals.

Melting point 223-224°C.

Elemental analysis for  $C_{25}H_{34}N_4O_6 \cdot 0.25H_2O$

Calculated: C, 61.15; H, 7.08; N, 11.41.

5 Found: C, 61.00; H, 7.11; N, 11.13.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.86 (6H, d,  $J=6.6$  Hz), 0.98 (3H, t,  $J=7.3$  Hz), 1.42 (9H, s), 1.43-1.61 (2H, m), 1.76-1.90 (2H, m), 2.04-2.15 (1H, m), 3.86-3.92 (4H, m), 4.39 (2H, d,  $J=4.4$  Hz), 7.36 (1H, bs), 7.94 (1H, dd,  $J=1.4$ , 8.4 Hz), 8.15 (1H, d,  $J=1.4$  Hz), 8.38 (1H, d,  $J=8.4$  Hz).

10 (3) Tert-butyl [4-butoxy-2-isobutyl-1-oxo-6-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.44 g, 0.9 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (10 ml) and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the obtained crystals were recrystallized from methanol - diethyl ether to give 3-(aminomethyl)-4-butoxy-2-isobutyl-6-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-1(2H)-isoquinolinone hydrochloride (0.36 g, 94.7%) as crystals. Melting point 256-258°C.

Elemental analysis for  $C_{20}H_{27}N_4O_4Cl \cdot 0.25H_2O$

Calculated: C, 56.20; H, 6.49; N, 13.11.

25 Found: C, 56.23; H, 6.65; N, 12.98.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.90 (6H, d,  $J=6.4$  Hz), 1.01 (3H, t,  $J=7.3$  Hz), 1.46-1.64 (2H, m), 1.83-2.16 (3H, m), 3.95-4.02 (4H, m), 4.21 (2H, s), 8.03 (1H, dd,  $J=1.8$ , 8.4 Hz), 8.21 (1H, d,  $J=1.8$  Hz), 8.43 (1H, d,  $J=8.4$  Hz), 8.68 (3H, bs).

#### Example 203

3-(Aminomethyl)-4-butoxy-2-isobutyl-6-(5-methyl-1,2,4-oxadiazol-3-yl)-1(2H)-isoquinolinone hydrochloride

(1) A solution of tert-butyl [6-amino(hydroxyimino)methyl]-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.46 g, 1

mmol), acetic anhydride (0.14 ml, 1.5 mmol) and a catalytic amount of acetic acid in tetrahydrofuran (10 ml) was refluxed under heating for 10 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was crystallized from ethyl acetate - diisopropyl ether to give tert-butyl [4-butoxy-2-isobutyl-6-(5-methyl-1,2,4-oxadiazol-3-yl)-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.22 g, 45.8%) as crystals.

Melting point 151.5-152°C.

Elemental analysis for  $C_{26}H_{36}N_4O_6$

Calculated: C, 64.44; H, 7.49; N, 11.56.

15 Found: C, 64.12; H, 7.74; N, 11.54.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.98 (6H, d,  $J=6.6$  Hz), 1.05 (3H, t,  $J=7.3$  Hz), 1.47 (9H, s), 1.56-1.68 (2H, m), 1.86-1.95 (2H, m), 2.15-2.24 (1H, m), 2.70 (3H, s), 3.92 (2H, t,  $J=6.6$  Hz), 4.02 (2H, d,  $J=7.5$  Hz), 4.54 (2H, d,  $J=5.7$  Hz), 4.78 (1H, bs), 8.15 (1H, dd,  $J=1.8, 8.7$  Hz), 8.42 (1H, d,  $J=1.8$  Hz), 8.51 (1H, d,  $J=8.7$  Hz).

(2) Tert-butyl [4-butoxy-2-isobutyl-6-(5-methyl-1,2,4-oxadiazol-3-yl)-1-oxo-1,2-dihydro-3-isoquinolinyl]-methylcarbamate (0.15 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the obtained crystals were recrystallized from methanol - diethyl ether to give 3-(aminomethyl)-4-butoxy-2-isobutyl-6-(5-methyl-1,2,4-oxadiazol-3-yl)-1(2H)-isoquinolinone hydrochloride (0.11 g, 91.7%) as crystals.

Melting point 230-232°C.

Elemental analysis for  $C_{21}H_{29}N_4O_3Cl \cdot 0.25H_2O$

35 Calculated: C, 59.29; H, 6.99; N, 13.17.

Found: C, 59.50; H, 7.02; N, 12.95.



<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.90 (6H, d, J=6.6 Hz), 1.03 (3H, t, J=7.3 Hz), 1.52-1.67 (2H, m), 1.70-1.99 (2H, m), 2.02-2.12 (1H, m), 2.73 (3H, s), 3.95-4.02 (4H, m), 4.22 (2H, s), 8.18 (1H, d, J=8.4 Hz), 8.39 (1H, s), 8.45 (1H, d, J=8.4 Hz), 8.67 (3H, bs).

#### Example 204

3-(Aminomethyl)-4-butoxy-2-isobutyl-6-(1H-tetrazol-5-yl)-1(2H)-isoquinolinone hydrochloride

(1) A solution of tert-butyl [4-butoxy-6-cyano-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.85 g, 2 mmol), triethylamine hydrochloride (0.34 g, 2.5 mmol) and sodium azide (0.16 g, 2.5 mmol) in toluene (20 ml) was stirred at 90°C for 24 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crystals were recrystallized from tetrahydrofuran - diisopropyl ether to give tert-butyl [4-butoxy-2-isobutyl-1-oxo-6-(1H-tetrazol-5-yl)-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.50 g, 53.2%) as crystals.

Melting point 152-153°C.

Elemental analysis for C<sub>24</sub>H<sub>34</sub>N<sub>6</sub>O<sub>4</sub> · 0.25H<sub>2</sub>O

Calculated: C, 60.68; H, 7.32; N, 17.69.

Found: C, 60.98; H, 7.20; N, 17.29.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.95-1.02 (9H, m), 1.48-1.61 (11H, m), 1.81-1.92 (2H, m), 2.14-2.27 (1H, m), 3.91 (2H, t, J=6.6 Hz), 4.08 (2H, d, J=7.2 Hz), 4.57 (2H, d, J=5.2 Hz), 4.79 (1H, bs), 5.39 (1H, bs), 8.12 (1H, dd, J=1.5, 8.5 Hz), 8.40 (1H, d, J=8.5 Hz), 8.46 (1H, d, J=1.5 Hz).

(2) Tert-butyl [4-butoxy-2-isobutyl-1-oxo-6-(1H-tetrazol-5-yl)-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.47 g, 1 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room

temperature for 1 h. The reaction was concentrated under reduced pressure and the obtained crystals crystallized from methanol - diethyl ether to give 3-(aminomethyl)-4-butoxy-2-isobutyl-6-(1H-tetrazol-5-yl)-1(2H)-isoquinolinone hydrochloride (0.38 g, 92.7%) as crystals.

Melting point 252-254°C.

Elemental analysis for  $C_{19}H_{27}N_6O_2Cl \cdot 0.25H_2O$

Calculated: C, 55.47; H, 6.74; N, 20.43.

10 Found: C, 55.63; H, 6.67; N, 20.21.

$^1H$ -NMR(DMSO- $d_6$ ),  $\delta$ : 0.91 (6H, d,  $J=7.0$  Hz), 1.02 (3H, t,  $J=7.3$  Hz), 1.50-1.69 (2H, m), 1.85-2.10 (3H, m), 3.98-4.02 (4H, m), 4.22 (2H, s), 8.30 (1H, dd,  $J=1.4, 8.4$  Hz), 8.48 (1H, d,  $J=8.4$  Hz), 8.51 (1H, d,  $J=1.4$  Hz), 8.63 (3H, bs).

#### Example 205

2-(Aminomethyl)-4-isobutyl-5-phenyl[1,7]naphthyridin-8(7H)-one dihydrochloride

(1) To a suspension of 3-benzoylpyridin-2-carboxylic acid (2.27 g, 10 mmol) in toluene (20 ml) was added thionyl chloride (0.88 ml, 12 mmol) and the mixture was stirred at 100°C for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in tetrahydrofuran (20 ml). The obtained solution was added dropwise to (isobutylamino)-acetonitrile (1.68 g, 15 mmol) in N,N-dimethylacetamide (20 ml) and the mixture was stirred at 70°C for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. To a solution of the residue and acetic anhydride (1.1 ml, 12 mmol) in acetonitrile (30 ml) was added 1,8-diazabicyclo[5.4.0]-7-undecene (6.0 ml, 40 mmol) at 0°C and the mixture was stirred at room temperature for 15 h. Water was added to the reaction mixture and the mixture was stirred at room

temperature for 30 min. The precipitated crystals were collected by filtration. The obtained crystals were recrystallized from tetrahydrofuran - diisopropyl ether to give 7-isobutyl-8-oxo-5-phenyl-7,8-

- 5 dihydro[1,7]naphthyridine-6-carbonitrile (2.65 g, 87.5%) as crystals.

Melting point 221-222°C.

Elemental analysis for  $C_{19}H_{17}N_3O$

Calculated: C, 75.23; H, 5.65; N, 13.85.

- 10 Found: C, 75.20; H, 5.72; N, 13.85.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.06 (6H, d,  $J=7.0$  Hz), 2.30-2.51 (1H, m), 4.24 (2H, d,  $J=7.8$  Hz), 7.37-7.46 (2H, m), 7.52-7.61 (4H, m), 7.72 (1H, dd,  $J=1.8, 8.3$  Hz), 9.01 (1H, dd,  $J=1.8, 8.4$  Hz).

- 15 (2) A suspension of 7-isobutyl-8-oxo-5-phenyl-7,8-dihydro[1,7]naphthyridine-6-carbonitrile (2.43 g, 8 mmol), Raney-cobalt (2.4 ml) and 25% aqueous ammonia (3.2 ml) in tetrahydrofuran (100 ml) was stirred under a hydrogen atmosphere at 5 atm and 60°C for 3 h. Raney-
- 20 cobalt was filtered off and the filtrate was

concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (30 ml) and to the obtained solution was added di-*t*-butyl dicarbonate (2.3 ml, 10 mmol). The mixture was stirred at room temperature for

- 25 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give
- 30 tert-butyl (7-isobutyl-8-oxo-5-phenyl-7,8-dihydro[1,7]naphthyridin-6-yl)methylcarbamate (0.21 g, 6.4%) as crystals.

Melting point 176-177°C.

Elemental analysis for  $C_{24}H_{29}N_3O_3$

- 35 Calculated: C, 70.74; H, 7.17; N, 10.31.

Found: C, 70.59; H, 7.18; N, 10.26.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.01 (6H, d, J=6.6 Hz), 1.44 (9H, s), 2.23-2.32 (1H, m), 4.14 (2H, d, J=7.2 Hz), 4.22 (2H, d, J=5.4 Hz), 4.93 (1H, bs), 7.26-7.33 (4H, m), 7.45-7.57 (3H, m), 8.76-8.77 (1H, m).

5 (3) Tert-butyl (7-isobutyl-8-oxo-5-phenyl-7,8-dihydro[1,7]naphthyridin-6-yl)methylcarbamate (0.16 g, 0.4 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml) and the mixture was stirred at room temperature for 1 h. The reaction  
10 mixture was concentrated under reduced pressure and the obtained crystals were recrystallized from methanol - ethyl acetate to give 2-(aminomethyl)-4-isobutyl-5-phenyl[1,7]naphthyridin-8(7H)-one dihydrochloride (0.12 g, 80.0%) as crystals.

15 Melting point 293°C.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.94 (6H, d, J=6.6 Hz), 2.06-2.19 (1H, m), 3.91 (2H, d, J=3.9 Hz), 4.14 (2H, d, J=7.2 Hz), 7.41-7.44 (3H, m), 7.50-7.62 (3H, m), 7.71-7.76 (1H, m), 8.79 (3H, bs), 8.88-8.90 (1H, m).

20 **Example 206**

3-(Aminomethyl)-2-isobutyl-6-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-4-phenyl-1(2H)-isoquinolinone hydrochloride

(1) To a mixture of tert-butyl (6-cyano-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate  
25 (0.86 g, 2.0 mmol), hydroxylamine hydrochloride (0.21 g, 3.0 mmol) and ethanol (20 mL) was added potassium t-butoxide (0.34 g, 3.0 mmol) at room temperature and the mixture was stirred at 75-80°C for 3 h. The reaction  
30 mixture was poured into water (100 mL) and the mixture was extracted with ethyl acetate (50 mL). The organic layer was washed with saturated brine (20 mL) and dried over anhydrous magnesium sulfate (6 g). The solvent was evaporated and the residue was purified by silica gel  
35 column chromatography (n-hexane-ethyl acetate=1:1 (v/v)) to give tert-butyl {6-[amino(hydroxyimino)methyl]-2-

isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)methylcarbamate (0.57 g, 62%) as a colorless powder.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.90 (6H, d, J=6.6 Hz), 1.38 (9H, s), 2.05-2.20 (1H, m), 3.85-4.00 (4H, s), 5.84 (2H, bs),  
5 7.29 (1H, d, J=1.8 Hz), 7.31 (1H, br), 7.35-7.55 (5H, m), 7.55 (1H, dd, J= 1.8, 8.4 Hz), 9.83 (1H, s).

(2) Tert-butyl {6-[amino(hydroxyimino)methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)methylcarbamate (0.25 g, 0.54 mmol) was dissolved in  
10 ethyl acetate (10 mL) and N,N'-carbonyldiimidazole (0.26 g, 1.6 mmol) was added. The mixture was refluxed under heating for 3 h. To the reaction mixture were added 0.1 M aqueous citric acid solution (25 mL) and ethyl acetate (50 mL). The organic layer was washed with 0.1 M  
15 aqueous citric acid solution (25 mL), and then saturated brine (25 mL), dried over anhydrous magnesium sulfate (12 g) and concentrated under reduced pressure. The residue was recrystallized from diisopropyl ether-ethyl acetate=2:1 (v/v) to give tert-butyl [2-isobutyl-1-oxo-  
20 6-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.24 g, 93%) as a colorless powder.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.01 (6H, d, J=6.6 Hz), 1.44 (9H, s), 2.15-2.35 (1H, m), 4.10 (2H, d, J=7.2 Hz), 4.22 (2H, d, J=5.4 Hz), 4.64 (1H, br), 7.25-7.35 (3H, m), 7.45-7.60  
25 (3H, m), 7.82 (1H, dd, J=1.7, 8.4 Hz), 8.52 (1H, d, J=8.4 Hz).

(3) Tert-butyl [2-isobutyl-1-oxo-6-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.18 g, 0.37 mmol) was  
30 dissolved in ethanol (4 mL) and a solution (4 mL) of 4N hydrogen chloride in ethyl acetate was added. The mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure,  
35 and the residue was washed with diisopropyl ether (2 mL) and recrystallized from ethyl acetate-ethanol (20:1) to

give 3-(aminomethyl)-2-isobutyl-6-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-4-phenyl-1(2H)-isoquinolinone hydrochloride (0.12 g, 80%) as a colorless powder.

Elemental analysis for  $C_{22}H_{22}N_4O_3 \cdot HCl \cdot 0.5H_2O$ ,

5 Calculated: C, 60.62; H, 5.55; N, 12.85.

Found: C, 61.01; H, 5.49; N, 12.21.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.93 (6H, d,  $J=6.6$  Hz), 2.00-2.25 (1H, m), 3.88 (2H, s), 4.08 (2H, d,  $J=7.2$  Hz), 7.35-7.45 (3H, m), 7.55-7.65 (3H, m), 7.96 (1H, dd,  $J=1.8, 8.4$  Hz),

10 8.46 (3H, br), 8.50 (1H, d,  $J=8.4$  Hz).

Melting point: 253°C (decomposition)

#### Example 207

3-(Aminomethyl)-2-isobutyl-6-(5-oxo-4,5-dihydro-1,2,4-thiadiazol-3-yl)-4-phenyl-1(2H)-isoquinolinone

15 hydrochloride

(1) A mixture of tert-butyl {6-[amino(hydroxyimino)methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl}methylcarbamate (0.50 g, 1.1 mmol), acetic acid (5 mL) and acetic anhydride (0.12 mL, 1.3 mmol) was stirred at room temperature for 20 min.

To the reaction mixture was added 10% palladium-activated carbon (0.05 g) under a nitrogen atmosphere and the mixture was stirred at room temperature and 1 atm under a hydrogen atmosphere for 12 h. The insoluble material was filtered off and the solvent was evaporated.

Diisopropyl ether (2 mL) was added to the residue to give tert-butyl {6-[amino(imino)methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl}methylcarbamate diacetate (0.92 g, 85%) as a brown powder.

30  $^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.90 (6H, d,  $J=6.6$  Hz), 1.38 (9H, s), 1.80 (6H, s), 2.05-2.25 (1H, m), 3.90-4.05 (4H, m), 7.23 (1H, d,  $J=1.4$  Hz), 7.30-7.45 (3H, m), 7.45-7.60 (3H, m), 7.76 (1H, dd,  $J=1.4, 8.2$  Hz), 8.44 (1H, d,  $J=8.2$  Hz), 10.59 (2H, br).

35 (2) Chlorocarbonylsulphenyl chloride (0.04 mL, 0.45 mmol) was added to a mixture of tert-butyl {6-

[amino(imino)methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)methylcarbamate diacetate (0.25 g, 0.43 mmol), sodium carbonate (0.40 g, 3.8 mmol), water (5 mL) and tetrahydrofuran (5 mL) while stirring vigorously under ice-cooling. The reaction mixture was stirred for 3 h, warmed to room temperature and stirred for 1 h more. The reaction mixture was added to 1N hydrochloric acid (30 mL) and extracted twice with ethyl acetate (30 mL). The organic layers were combined and washed with 1N hydrochloric acid (10 mL) and then saturated brine (10 mL), dried over anhydrous magnesium sulfate (12 g) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane-ethyl acetate=1:1 (v/v)) to give tert-butyl [2-isobutyl-1-oxo-6-(5-oxo-4,5-dihydro-1,2,4-thiadiazol-3-yl)-4-phenyl-1,2-dihydro-3-isoquinoliny]methylcarbamate (0.084 g, 39%) as a yellow powder.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.01 (6H, d, J=6.6 Hz), 1.44 (9H, s), 2.15-2.35 (1H, m), 4.03 (2H, d, J=6.6 Hz), 4.19 (2H, d, J=5.2 Hz), 4.73 (1H, br), 7.25-7.35 (3H, m), 7.50-7.60 (3H, m), 7.97 (1H, dd, J=1.8, 8.4 Hz), 8.53 (1H, d, J=8.4 Hz), 11.44 (1H, bs).

(3) Tert-butyl [2-isobutyl-1-oxo-6-(5-oxo-4,5-dihydro-1,2,4-thiadiazol-3-yl)-4-phenyl-1,2-dihydro-3-isoquinoliny]methylcarbamate (0.050 g, 0.10 mmol) was dissolved in tetrahydrofuran (3 mL) and a solution (2 mL) of 4N hydrogen chloride in ethyl acetate was added. The mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated under reduced pressure and diisopropyl ether-ethyl acetate (2:1) was added to the residue to give 3-(aminomethyl)-2-isobutyl-6-(5-oxo-4,5-dihydro-1,2,4-thiadiazol-3-yl)-4-phenyl-1(2H)-isoquinolinone hydrochloride (0.041 g, 94%) as a pale-yellow powder.

Elemental analysis for C<sub>22</sub>H<sub>22</sub>N<sub>4</sub>O<sub>2</sub>S HCl 0.75H<sub>2</sub>O,

Calculated: C, 57.89; H, 5.41; N, 12.27.

Found: C, 57.95; H, 5.41; N, 11.58.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.95 (6H, d, J=6.6 Hz), 2.00-2.20 (1H, m), 3.93 (2H, s), 4.09 (2H, d, J=7.4 Hz), 7.35-7.50 (2H, m), 7.50-7.65 (3H, m), 7.86 (1H, d, J=1.8 Hz), 8.32 (1H, dd, J=1.8, 8.2 Hz), 8.48 (1H, d, J=8.2 Hz), 8.50 (3H, bs).

Melting point: 232-237°C

#### Example 208

#### 10 6-Bromo-2-isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinoline-3-carbonitrile

To a mixture of 2-benzoyl-4-bromobenzoic acid (5.0 g), toluene (65 ml) and dimethylformamide (0.1 ml) was added dropwise thionyl chloride (1.42 ml) under a nitrogen atmosphere, and the mixture was stirred at 50°C for 1.5 h. The solvent was evaporated and toluene (10 ml) was added to the residue. The mixture was heated to around 90°C. Diisopropylethylamine (4.21 ml) was added to the obtained solution and the mixture was stirred for about 5 min. Isobutylaminoacetonitrile (2.75 g) was added and the mixture was stirred at around the same temperature for 3 h. The reaction mixture was cooled to 25°C and 1N hydrochloric acid (50 ml) was added and stirred. The organic layer was separated and washed with 10% brine (50 ml). The solvent was evaporated to give 2-benzoyl-4-bromo-(N-cyanomethyl)-N-(isobutyl)benzamide. Acetonitrile (15 ml) and ethanol (15 ml) were added to the residue, and acetic anhydride (1.85 ml) and 1,8-diazabicyclo[5,4,0]-7-undecene (4.90 ml) were successively added dropwise to the mixture below 40°C. The reaction mixture was heated to 50°C and the mixture was stirred for 1 h. The reaction mixture was cooled to around 25°C and water (12.5 ml) was added dropwise. The mixture was stirred at the same temperature for 1 h. The precipitated crystals were collected by filtration and washed with 70% ethanol to



give the title compound (5.31 g, yield 85%).

<sup>1</sup>H-NMR(300MHz, CDCl<sub>3</sub>) δ:1.04(6H, d, J=6.7Hz), 2.30-2.39(1H, m), 4.15(2H, d, J=7.5Hz), 7.39-7.44(3H, m), 7.55-7.60(3H, m), 7.76(1H, dd, J=1.9Hz, 8.6Hz), 8.39(1H, d, J=8.6Hz)

**Example 209**

3-(Aminomethyl)-6-bromo-2-isobutyl-4-phenylisoquinolin-1(2H)-one

A mixture of 6-bromo-2-isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinoline-3-carbonitrile (16.0 g), sponge cobalt (manufactured by Kawaken Fine Chemicals Co., Ltd.; trademark: ODHT-60) (4 ml), 25% ammonium hydroxide (2 ml) and tetrahydrofuran (80 ml) was stirred at 60°C at a 1 MPa hydrogen pressure for 4 h and the catalyst was filtered off. The solvent was evaporated and acetonitrile (48 ml) was added to the residue. The mixture was heated to about 70°C. The obtained solution was cooled to 25°C to give crystals, and water (80 ml) was added dropwise. The obtained mixture was cooled to around 5°C and the mixture was stirred for 1 h. The precipitated crystals were collected by filtration to give the title compound (14.8 g, yield 91.4%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:1.00(6H, d, J=6.7Hz), 1.10(2H, br), 2.25(1H, m), 3.65(2H, s), 4.20(2H, d, J=7.4Hz), 7.07(1H, d, J=1.9Hz), 7.08-7.28(2H, m), 7.45-7.54(4H, m), 8.32(1H, d, J=8.6Hz)

**Example 210**

3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinoline-6-carbonitrile

A mixture of 3-(aminomethyl)-6-bromo-2-isobutyl-4-phenylisoquinolin-1(2H)-one (15.0 g), zinc cyanide (2.74 g), tetrakis(triphenylphosphine)palladium (1.35 g), N-methylpyrrolidone (75 ml) and water (0.75 ml) was stirred under a nitrogen atmosphere at an inner temperature of 54-56°C. To the reaction mixture was added dropwise saturated aqueous ammonium chloride-25%

ammonium hydroxide-water (4:1:4, 37.5 ml) over 30 min at the same temperature, and the mixture was stirred for 1 h and below 5°C for 1 h. The obtained crystals were collected by filtration and suspended in acetonitrile (105 ml). The suspension was dissolved at 80°C. To the obtained solution was added activated carbon (0.75 g) and the mixture was stirred for 10 min. The activated carbon was filtered off and washed with acetonitrile (15 ml). The filtrate was combined and cooled to 25°C to give crystals. Water (120 ml) was added dropwise and the obtained mixture was cooled to 5°C and stirred for 1 h. The obtained crystals were collected by filtration to give the title compound (9.6 g, yield 74.5%).

<sup>1</sup>H-NMR(300MHz, CDCl<sub>3</sub>) δ:1.01(6H, d, J=6.8Hz), 1.13(2H, br), 2.22-2.31(1H, m), 3.69(2H, s), 4.23(2H, d, J=7.5Hz), 5.55-5.95(2H, br), 7.24-7.28(3H, m), 7.50-7.56(3H, m), 7.61(1H, dd, J=1.5Hz, 8.3Hz), 8.55(1H, d, J=8.3Hz)

#### Example 211

3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinoline-6-carboxamide 1/2 dimethyl sulfoxide solvate

A mixture of 3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinoline-6-carbonitrile (20.0 g), 2N aqueous sodium hydroxide solution (6 ml), dimethyl sulfoxide (100 ml) and water (40 ml) was stirred at an inner temperature of 85°C for 30 min. The reaction mixture was cooled to 40°C, cooled to not higher than 5°C and stirred for 1 h. The precipitated crystals were collected by filtration and washed twice with water (40 ml) to give the title compound (21.7 g) as pale yellow crystals.

<sup>1</sup>H-NMR(300MHz, CDCl<sub>3</sub>) δ:1.01(6H, d, J=6.7Hz), 2.20-2.32(1H, m), 2.62(6H, s; DMSO), 3.68(2H, s), 4.24(2H, d, J=7.4Hz), 5.55-5.95(2H, br), 7.25-7.30(2H, m), 7.39(1H, d, J=1.6Hz), 7.45-7.55(3H, m), 7.79(1H, dd, J=1.5Hz, 8.3Hz), 8.54(1H, d, J=8.3Hz)

**Example 212**

3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinoline-6-carboxamide

A mixture of 3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinoline-6-carboxamide (10 g), methanol (40 ml) and 1N hydrochloric acid (20 ml) was heated to 60°C. 1N Hydrochloric acid (ca. 7 ml) was added to the reaction mixture at around the same temperature to adjust pH to 2.0, and activated carbon (0.5 g) was added. The mixture was stirred for about 10 min and activated carbon was filtered off. The obtained solution was washed with methanol-water (2:1) (10 ml) and heated again to around 60°C with stirring. 5% Ammonium hydroxide was added to the reaction mixture while keeping the same temperature to adjust pH to 7.3, and water (10 ml) was added dropwise. The obtained mixture was cooled to 25°C, ice-cooled and stirred at around 5°C for 1 h. The precipitated crystals (8.48 g) were collected by filtration, suspended in ethyl acetate (85 ml) and stirred at around 75°C for 2 h. The obtained mixture was allowed to cool for 1 h, ice-cooled and stirred at around 5°C for 1 h. The precipitated crystals were collected by filtration and washed with previously-cooled ethyl acetate (17 ml) to give the title compound as crystals (8.02 g).

Powder X-ray crystal diffraction data

Diffraction angle:  $2\theta(^{\circ})$       spacing: d value (angstrom)

	8.96	9.86
30	13.7	6.46
	15.9	5.56
	16.6	5.34
	22.8	3.89
	24.4	3.65
35	24.7	3.60
	25.3	3.52

25.7

3.46

**Example 213**

7-(Aminomethyl)-6-isobutyl-8-phenyl[1,3]dioxolo[4,5-g]isoquinolin-5(6H)-one

5 This compound was synthesized according to the method similar to that in Example 106.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.99 (6H, d, J = 6.6 Hz), 1.32 (2H, br), 2.26 (1H, m), 3.64 (2H, s), 4.19 (2H, d, J = 7.6 Hz), 6.00 (2H, s), 6.29 (1H, s), 7.23-7.28 (2H, m), 7.40-7.54 (3H, m), 7.83 (1H, s).

**Example 214**

Ethyl 2-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxylate hydrochloride

15 (1) A solution of 9H-fluoren-9-ylmethyl [6-(aminocarbothioyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (1.76 g, 3 mmol) and ethyl 2-chloroacetate (0.99 g, 6 mmol) in ethanol (20 ml) was refluxed under heating for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give ethyl 2-[3-  
25 ({[(9H-fluoren-9-ylmethoxy)carbonyl]amino)methyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxylate (1.46 g, 69.9%) as crystals.

Melting point 157-158°C.

30 Elemental analysis for C<sub>42</sub>H<sub>39</sub>N<sub>3</sub>O<sub>5</sub>S

Calculated: C, 72.29; H, 5.63; N, 6.02.

Found: C, 72.12; H, 5.69; N, 5.79.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.99 (6H, d, J = 6.9 Hz), 1.37 (3H, t, J = 7.2 Hz), 2.12-2.29 (1H, m), 2.69 (3H, s), 4.08 (2H, d, J = 6.0 Hz), 4.21 (1H, t, J = 6.9 Hz), 4.26 (2H, d, J = 4.8 Hz), 4.33 (2H, q, J = 7.2 Hz), 4.44 (2H, d, J = 6.9 Hz),

5.23 (1H, bs), 7.26-7.45 (7H, m), 7.51-7.60 (5H, m), 7.75 (2H, d, J=7.5 Hz), 7.97 (1H, d, J=8.4 Hz), 8.46 (1H, d, J=8.4 Hz).

(2) To a solution of ethyl 2-[3-({[(9H-fluoren-9-ylmethoxy)carbonyl]amino}methyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxylate (1.40 g, 2 mmol) in N,N-dimethylformamide (20 ml) was added pyridine (1 ml). The mixture was stirred at room temperature for 1 h.  
10 The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 ml), and di-t-butyl dicarbonate  
15 (0.69 ml, 3 mmol) was added thereto. The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated  
20 under reduced pressure. The residue was purified by silica gel column chromatography to give ethyl 2-(3-({[(tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)-4-methyl-1,3-thiazole-5-carboxylate (0.88 g, 76.5%) as crystals.

25 Melting point 201-202°C.

Elemental analysis for  $C_{30}H_{37}N_3O_5S$

Calculated: C, 66.76; H, 6.48; N, 7.30.

Found: C, 66.85; H, 6.56; N, 7.27.

$^1H$ -NMR(CDCl<sub>3</sub>)  $\delta$ : 1.02 (6H, d, J=6.6 Hz), 1.37 (3H, t, J=7.0 Hz), 1.44 (9H, s), 2.18-2.32 (1H, m), 2.71 (3H, s),  
30 4.19 (2H, d, J=7.4 Hz), 4.22 (2H, d, J=5.6 Hz), 4.33 (2H, q, J=7.0 Hz), 4.69 (1H, bs), 7.28-7.34 (2H, m), 7.46 (1H, d, J=1.6 Hz), 7.51-7.62 (3H, m), 8.00 (1H, dd, J=1.6, 8.4 Hz), 8.49 (1H, d, J=8.4 Hz).

35 (3) Ethyl 2-(3-({[(tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)-4-

methyl-1,3-thiazole-5-carboxylate (0.14 g, 0.5 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the precipitated crystals were recrystallized from methanol - diisopropyl ether to give ethyl 2-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxylate hydrochloride (0.11 g, 91.7%) as crystals.

Melting point 286-287°C.

Elemental analysis for  $C_{27}H_{30}N_3O_3ClS \cdot 0.25H_2O$

Calculated: C, 62.78; H, 5.95; N, 8.13.

Found: C, 62.94; H, 6.35; N, 8.11.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.94 (6H, d,  $J=6.6$  Hz), 1.29 (3H, t,  $J=7.2$  Hz), 2.02-2.21 (1H, m), 2.63 (3H, s), 3.90 (2H, s), 4.10 (2H, d,  $J=7.8$  Hz), 4.28 (2H, q,  $J=7.2$  Hz), 7.44-7.52 (3H, m), 7.61-7.65 (3H, m), 8.14 (1H, dd,  $J=1.6$ , 8.4 Hz), 8.46 (1H, d,  $J=8.4$  Hz), 8.59 (3H, bs).

#### Example 215

2-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxylic acid hydrochloride

(1) To a solution of ethyl 2-(3-[(tert-butoxycarbonyl)amino]methyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)-4-methyl-1,3-thiazole-5-carboxylate (0.69 g, 1.2 mmol) in tetrahydrofuran (10 ml) and ethanol (10 ml) was added 1N sodium hydroxide solution (3 ml). The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was crystallized from ethyl acetate - n-hexane to give 2-(3-[(tert-butoxycarbonyl)amino]methyl)-2-isobutyl-1-oxo-4-

phenyl-1,2-dihydro-6-isoquinolinyl)-4-methyl-1,3-thiazole-5-carboxylic acid (0.61 g, 93.8%) as crystals. Melting point 184-186°C.

Elemental analysis for  $C_{30}H_{33}N_3O_5S$

5 Calculated: C, 65.79; H, 6.07; N, 7.67.

Found: C, 65.60; H, 6.23; N, 7.46.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.01 (6H, d,  $J=6.6$  Hz), 1.50 (9H, s), 2.14-2.28 (1H, m), 2.67 (3H, s), 4.08 (2H, d,  $J=6.6$  Hz), 4.17 (2H, s), 5.84 (1H, bs), 7.38-7.44 (2H, m), 7.51-  
10 7.71 (5H, m), 8.28 (1H, d,  $J=8.8$  Hz).

(2) 2-(3-((Tert-butoxycarbonyl)amino)methyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)-4-methyl-1,3-thiazole-5-carboxylic acid (0.17 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in  
15 ethyl acetate (5 ml). The solution was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate to give 2-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-  
20 isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxylic acid hydrochloride (0.12 g, 92.3%) as crystals.

Melting point 239-241°C.

Elemental analysis for  $C_{25}H_{26}N_3O_3ClS \cdot H_2O$

Calculated: C, 59.82; H, 5.62; N, 8.37.

25 Found: C, 59.64; H, 5.46; N, 8.08.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.94 (6H, d,  $J=6.6$  Hz), 2.02-2.21 (1H, m), 2.61 (3H, s), 3.91 (2H, s), 4.10 (2H, d,  $J=8.8$  Hz), 7.44-7.49 (3H, m), 7.61-7.66 (3H, m), 8.12 (1H, dd,  $J=1.4, 8.4$  Hz), 8.45 (1H, d,  $J=8.4$  Hz), 8.64 (3H, bs).

30 **Example 216**

2-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxamide hydrochloride

(1) A solution of 2-(3-((tert-butoxycarbonyl)amino)methyl)-2-isobutyl-1-oxo-4-phenyl-  
35 1,2-dihydro-6-isoquinolinyl)-4-methyl-1,3-thiazole-5-

carboxylic acid (0.44 g, 0.8 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.31 g, 1.6 mmol) and 1-hydroxybenzotriazole ammonium salt (0.24 g, 1.6 mmol) in N,N-dimethylformamide (10 ml) was  
5 stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting crystals were  
10 recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl {6-[5-(aminocarbonyl)-4-methyl-1,3-thiazol-2-yl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.38 g, 86.4%) as crystals.

15 Melting point 227-228°C.

Elemental analysis for  $C_{30}H_{34}N_4O_4S$

Calculated: C, 65.91; H, 6.27; N, 10.25.

Found: C, 65.70; H, 6.19; N, 10.35.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.01 (6H, d,  $J=6.4$  Hz), 1.45 (9H, s),  
20 2.12-2.31 (1H, m), 2.66 (3H, s), 4.08 (2H, d,  $J=7.4$  Hz), 4.20 (2H, d,  $J=5.2$  Hz), 5.00 (1H, bs), 5.84 (2H, bs), 7.31-7.37 (3H, m), 7.52-7.61 (3H, m), 7.92 (1H, dd,  $J=1.6, 8.4$  Hz), 8.41 (1H, d,  $J=8.4$  Hz).

(2) Tert-butyl {6-[5-(aminocarbonyl)-4-methyl-1,3-thiazol-2-yl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.14 g, 0.25 mmol) was  
25 dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 1h. The reaction was concentrated under  
30 reduced pressure, and the resulting crystals were recrystallized from methanol - ethyl acetate to give 2-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxamide hydrochloride (0.11 g, 91.7%) as crystals.

35 Melting point 222-224°C.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.94 (6H, d,  $J=6.6$  Hz), 2.02-2.21 (1H,



m), 2.56 (3H, s), 3.89 (2H, s), 4.10 (2H, d, J=6.4 Hz), 7.42-7.49 (3H, m), 7.61-7.78 (5H, m), 8.09 (1H, d, J=8.6 Hz), 8.46 (1H, d, J=8.6 Hz), 8.54 (3H, bs).

#### Example 217

- 5 2-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carbonitrile hydrochloride

(1) A solution of tert-butyl [6-[5-(aminocarbonyl)-4-methyl-1,3-thiazol-2-yl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.16 g, 0.3 mmol) and cyanuric chloride (0.17 g, 0.9 mmol) in N,N-dimethylformamide (10 mmol) was stirred at 0°C for 1 h. The resulting reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [6-(5-cyano-4-methyl-1,3-thiazol-2-yl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.15 g, 93.8%) as crystals.

Melting point 209-211°C.

Elemental analysis for  $C_{30}H_{32}N_4O_3S$

Calculated: C, 68.16; H, 6.10; N, 10.60.

25 Found: C, 68.17; H, 5.99; N, 10.70.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.04 (6H, d, J=6.6 Hz), 1.44 (9H, s), 2.14-2.36 (1H, m), 2.61 (3H, s), 4.10 (2H, d, J=7.2 Hz), 4.23 (2H, d, J=5.4 Hz), 4.63 (1H, bs), 7.27-7.32 (2H, m), 7.42 (1H, d, J=1.5 Hz), 7.53-7.60 (3H, m), 7.97 (1H, dd, J=1.5, 8.4 Hz), 8.52 (1H, d, J=8.4 Hz).

(2) Tert-butyl [6-(5-cyano-4-methyl-1,3-thiazol-2-yl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.21 g, 0.4 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 1 h. The reaction mixture was

concentrated under reduced pressure, and the residue was crystallized from ethyl acetate to give 2-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carbonitrile

5 hydrochloride (0.11 g, 91.7%) as crystals.

Melting point 284-285°C.

Elemental analysis for  $C_{25}H_{25}N_4OClS \cdot 0.25H_2O$

Calculated: C, 63.95; H, 5.47; N, 11.93.

Found: C, 64.00; H, 5.45; N, 11.73.

10  $^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.94 (6H, d,  $J=6.6$  Hz), 2.06-2.21 (1H, m), 2.54 (3H, s), 3.89 (2H, s), 4.11 (2H, d,  $J=7.6$  Hz), 7.44-7.49 (2H, m), 7.52 (1H, d,  $J=1.5$  Hz), 7.60-7.63 (3H, m), 8.11 (1H, dd,  $J=1.5, 8.4$  Hz), 8.48 (1H, d,  $J=8.4$  Hz), 8.63 (3H, bs).

15 **Example 218**

Ethyl 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxylate hydrochloride

(1) A solution of 9H-fluoren-9-ylmethyl [6-(aminocarbothioyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (2.33 g, 4 mmol) and ethyl 2-chloroacetate (1.32 g, 8 mmol) in ethanol (20 ml) was refluxed under heating for 10 h. The resulting reaction mixture was poured into water and  
25 extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give  
30 ethyl 2-[4-butoxy-3-({[(9H-fluoren-9-ylmethoxy)carbonyl]amino}methyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxylate (1.81 g, 65.3%) as crystals.

Melting point 203-204°C.

Elemental analysis for  $C_{40}H_{43}N_3O_6S$

35 Calculated: C, 69.24; H, 6.25; N, 6.06.

Found: C, 69.08; H, 6.11; N, 5.99.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.97 (6H, d, J=6.6 Hz), 1.07 (3H, t, J=7.2 Hz), 1.42 (3H, t, J=7.2 Hz), 1.58-1.75 (2H, m), 1.84-1.97 (2H, m), 2.04-2.23 (1H, m), 2.81 (3H, s), 3.92 (2H, t, J=6.4 Hz), 4.00 (2H, d, J=7.2 Hz), 4.23 (1H, t, J=6.8 Hz), 4.39 (2H, q, J=7.2 Hz), 4.49 (2H, d, J=6.8 Hz), 4.59 (2H, d, J=5.6 Hz), 5.29 (1H, bs), 7.28-7.43 (4H, m), 7.60 (2H, d, J=7.4 Hz), 7.75 (2H, d, J=7.0 Hz), 8.05 (1H, dd, J=1.8, 8.4 Hz), 8.24 (1H, d, J=1.8 Hz), 8.44 (1H, d, J=8.4 Hz).

10 (2) To a solution of ethyl 2-[4-butoxy-3-({[(9H-fluoren-9-ylmethoxy)carbonyl]amino}methyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxylate (1.73 g, 2.5 mmol) in N,N-dimethylformamide (20 ml) and tetrahydrofuran (10 ml) was added  
15 pyrrolidine (2 ml). The resulting mixture was stirred at room temperature for 1 h. The reaction was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The  
20 residue was dissolved in tetrahydrofuran (20 ml), and di-t-butyl dicarbonate (0.9 ml, 3.8 mmol) was added thereto. The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract  
25 was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give ethyl 2-(4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl)-4-methyl-1,3-thiazole-5-carboxylate (1.15 g, 80.4%) as crystals.

Melting point 145.5-147°C.

Elemental analysis for C<sub>30</sub>H<sub>41</sub>N<sub>3</sub>O<sub>6</sub>S

Calculated: C, 63.02; H, 7.23; N, 7.35.

35 Found: C, 63.00; H, 7.30; N, 7.28.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.97 (6H, d, J=6.6 Hz), 1.08 (3H, t,

J=7.3 Hz), 1.41 (3H, t, J=7.2 Hz), 1.47 (9H, s), 1.57-1.76 (2H, m), 1.85-1.99 (2H, m), 2.08-2.24 (1H, m), 2.81 (3H, s), 3.92 (2H, t, J=6.4 Hz), 4.00 (2H, d, J=7.8 Hz), 4.38 (2H, q, J=7.2 Hz), 4.54 (2H, d, J=5.6 Hz), 4.87 (1H, bs), 8.05 (1H, dd, J=1.8, 8.6 Hz), 8.26 (1H, d, J=1.8 Hz), 8.46 (1H, d, J=8.6 Hz).

(3) Ethyl 2-(4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl)-4-methyl-1,3-thiazole-5-carboxylate (0.17 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate to give ethyl 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxylate hydrochloride (0.14 g, 93.3%) as crystals.

Melting point 250-254°C.

20 Elemental analysis for  $C_{25}H_{34}N_3O_4ClS$

Calculated: C, 59.10; H, 6.75; N, 8.27.

Found: C, 58.90; H, 6.84; N, 8.25.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.90 (6H, d, J=6.6 Hz), 1.05 (3H, t, J=7.1 Hz), 1.33 (3H, t, J=7.0 Hz), 1.57-1.76 (2H, m), 1.82-1.95 (2H, m), 1.00-2.18 (1H, m), 2.74 (3H, s), 3.97-4.00 (4H, m), 4.21 (2H, s), 4.33 (2H, q, J=7.0 Hz), 8.18 (1H, d, J=8.4 Hz), 8.32 (1H, s), 8.39 (1H, d, J=8.4 Hz), 8.67 (3H, bs).

#### Example 219

30 2-[3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxylic acid hydrochloride

(1) To a solution of ethyl 2-(4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl)-4-methyl-1,3-thiazole-5-carboxylate (0.91 g, 1.6 mmol) in tetrahydrofuran (5 ml)

and ethanol (5 ml) was added 1N sodium hydroxide solution (3 ml). The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting crystals were recrystallized from ethyl acetate - diisopropyl ether to give 2-(4-butoxy-3-((tert-butoxycarbonyl)amino)methyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl)-4-methyl-1,3-thiazole-5-carboxylic acid (0.78 g, 89.7%) as crystals.

Melting point 107-109°C.

Elemental analysis for  $C_{28}H_{37}N_3O_6S \cdot 0.5H_2O$

15 Calculated: C, 60.85; H, 6.93; N, 7.60.

Found: C, 60.73; H, 6.92; N, 7.41.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.96 (6H, d,  $J=6.6$  Hz), 1.11 (3H, t,  $J=7.3$  Hz), 1.52 (9H, s), 1.60-1.78 (2H, m), 1.87-2.01 (2H, m), 2.04-2.21 (1H, m), 2.82 (3H, s), 3.89-3.98 (4H, m), 4.54 (2H, d,  $J=4.8$  Hz), 5.71 (1H, bs), 7.91 (1H, d,  $J=8.3$  Hz), 8.10 (1H, s), 8.29 (1H, d,  $J=8.3$  Hz).

(2) 2-(4-Butoxy-3-((tert-butoxycarbonyl)amino)methyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl)-4-methyl-1,3-thiazole-5-carboxylic acid (0.16 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate to give 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxylic acid hydrochloride (0.13 g, 92.9%) as crystals.

Melting point 275-276°C.

Elemental analysis for. Calcd for  $C_{23}H_{30}N_3O_4ClS \cdot 0.25H_2O$

35 Calculated: C, 57.01; H, 6.34; N, 8.67.

Found: C, 57.03; H, 6.28; N, 8.51.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.90 (6H, d, J=6.6 Hz), 1.05 (3H, t, J=7.4 Hz), 1.59-1.72 (2H, m), 1.83-1.91 (2H, m), 1.99-2.16 (1H, m), 2.72 (3H, s), 3.98-4.06 (4H, m), 4.21 (2H, s), 8.18 (1H, d, J=8.1 Hz), 8.31 (1H, s), 8.39 (1H, d, J=8.1 Hz), 8.65 (3H, bs).

**Example 220**

2-[3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxamide hydrochloride

(1) A solution of 2-(4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl)-4-methyl-1,3-thiazole-5-carboxylic acid (0.60 g, 1.1 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.42 g, 2.2 mmol) and 1-hydroxybenzotriazole ammonium salt (0.33 g, 2.2 mmol) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting crystals were recrystallized from tetrahydrofuran - diisopropyl ether to give tert-butyl {6-[5-(aminocarbonyl)-4-methyl-1,3-thiazol-2-yl]-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.58 g, 96.7%) as crystals.

Melting point 233.5-234°C.

Elemental analysis for C<sub>28</sub>H<sub>38</sub>N<sub>4</sub>O<sub>4</sub>S

Calculated: C, 61.97; H, 7.06; N, 10.32.

Found: C, 61.95; H, 7.07; N, 10.19.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.97 (6H, d, J=6.6 Hz), 1.07 (3H, t, J=7.3 Hz), 1.49 (9H, s), 1.55-1.71 (2H, m), 1.80-1.98 (2H, m), 2.05-2.24 (1H, m), 2.78 (3H, s), 3.91 (2H, t, J=6.4 Hz), 3.99 (2H, d, J=7.4 Hz), 4.53 (2H, d, J=5.0 Hz), 5.05 (1H, bs), 5.94 (2H, bs), 7.98 (1H, dd, J=1.6, 8.6 Hz), 8.19 (1H, d, J=1.6 Hz), 8.42 (1H, d, J=8.6 Hz).

(2) Tert-butyl {6-[5-(aminocarbonyl)-4-methyl-1,3-thiazol-2-yl]-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.22 g, 0.4 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate to give 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carboxamide hydrochloride (0.18 g, 94.7%) as crystals.

Melting point 270-271°C.

Elemental analysis for  $C_{23}H_{31}N_4O_3ClS$

Calculated: C, 57.67; H, 6.52; N, 11.70.

Found: C, 57.37; H, 6.46; N, 11.62.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.90 (6H, d,  $J=6.6$  Hz), 1.05 (3H, t,  $J=7.1$  Hz), 1.56-1.74 (2H, m), 1.82-2.18 (3H, m), 2.67 (3H, s), 3.97-4.00 (4H, m), 4.21 (2H, s), 7.77 (2H, bs), 8.27 (1H, d,  $J=1.5$  Hz), 8.39 (1H, dd,  $J=1.5, 8.4$  Hz), 8.39 (1H, d,  $J=8.4$  Hz), 8.66 (3H, bs).

#### Example 221

2-[3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carbonitrile hydrochloride

(1) A solution of tert-butyl {6-[5-(aminocarbonyl)-4-methyl-1,3-thiazol-2-yl]-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.33 g, 0.6 mmol) and cyanuric chloride (0.33 g, 1.8 mmol) in N,N-dimethylformamide (10 mmol) was stirred for 1h at 0°C. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [4-butoxy-6-(5-cyano-4-methyl-1,3-thiazol-2-yl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.25

g, 80.6%) as crystals.

Melting point 148.5-149.5°C.

Elemental analysis for  $C_{28}H_{36}N_4O_4S$

Calculated: C, 64.10; H, 6.92; N, 10.68.

5 Found: C, 64.04; H, 6.96; N, 10.63.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.98 (6H, d,  $J=6.6$  Hz), 1.08 (3H, t,  $J=7.3$  Hz), 1.47 (9H, s), 1.57-1.75 (2H, m), 1.84-1.98 (2H, m), 2.08-2.28 (1H, m), 2.72 (3H, s), 3.91 (2H, t,  $J=6.4$  Hz), 4.01 (2H, d,  $J=7.4$  Hz), 4.54 (2H, d,  $J=5.6$  Hz), 4.80 (1H, bs), 8.02 (1H, dd,  $J=1.8, 8.2$  Hz), 8.24 (1H, d,  $J=1.8$  Hz), 8.48 (1H, d,  $J=8.2$  Hz).

(2) Tert-butyl [4-butoxy-6-(5-cyano-4-methyl-1,3-thiazol-2-yl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.21 g, 0.4 mmol) was  
15 dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate - diisopropyl ether to  
20 give 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-4-methyl-1,3-thiazole-5-carbonitrile hydrochloride (0.17 g, 94.4%) as crystals.

Melting point 166-168°C.

Elemental analysis for  $C_{23}H_{29}N_4O_2ClS \cdot 0.5H_2O$

25 Calculated: C, 58.77; H, 6.43; N, 11.92.

Found: C, 58.58; H, 6.45; N, 11.91.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.90 (6H, d,  $J=6.6$  Hz), 1.04 (3H, t,  $J=7.4$  Hz), 1.55-1.73 (2H, m), 1.82-1.95 (2H, m), 1.98-2.16 (1H, m), 2.66 (3H, s), 3.98-4.01 (4H, m), 4.22 (2H, s), 8.17 (1H, dd,  $J=1.8, 8.4$  Hz), 8.30 (1H, d,  $J=1.8$  Hz),  
30 8.42 (1H, d,  $J=8.4$  Hz), 8.69 (3H, bs).

#### Example 222

3-(Aminomethyl)-6-(4-amino-1,3-thiazol-2-yl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone dihydrochloride

35 (1) A solution of 2-(3-((tert-butoxycarbonyl)amino)methyl)-2-isobutyl-1-oxo-4-phenyl-



1,2-dihydro-6-isoquinoliny)-1,3-thiazole-4-carboxylic acid (1.60 g, 3 mmol), diphenylphosphoryl azide (0.78 ml, 3.6 mmol) and triethylamine (0.50 ml, 3.6 mmol) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in toluene (20 ml) and refluxed for 1 h. To the resulting mixture was added 9-fluorenylmethanol (0.88 g, 4.5 mmol), and the mixture was stirred at 100°C for 3 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 9H-fluoren-9-ylmethyl 2-(3-(((tert-butoxycarbonyl)amino)methyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinoliny)-1,3-thiazol-4-ylcarbamate (1.12 g, 51.4%) as an amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.01 (6H, d, J=6.6 Hz), 1.44 (9H, s), 2.19-2.32 (1H, m), 4.07 (2H, d, J=6.6 Hz), 4.11-4.22 (3H, m), 4.45 (2H, s), 4.63 (1H, bs), 7.24-7.56 (13H, m), 7.77 (2H, d, J=7.5 Hz), 7.88 (1H, d, J=7.8 Hz), 7.97 (1H, bs), 8.47 (1H, d, J=7.8 Hz).

(2) To a solution of 9H-fluoren-9-ylmethyl 2-(3-(((tert-butoxycarbonyl)amino)methyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinoliny)-1,3-thiazol-4-ylcarbamate (1.09 g, 1.5 mmol) in N,N-dimethylformamide (20 ml) was added pyrrolidine (1 ml). The mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [6-(4-amino-1,3-

thiazol-2-yl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.59 g, 78.7%) as crystals.

Melting point 195-196°C.

5 Elemental analysis for  $C_{28}H_{32}N_4O_3S \cdot 0.25H_2O$

Calculated: C, 66.05; H, 6.43; N, 11.00.

Found: C, 66.20; H, 6.54; N, 10.96.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.01 (6H, d,  $J=6.6$  Hz), 1.43 (9H, s),  
1.98-2.35 (1H, m), 4.08 (2H, d,  $J=7.8$  Hz), 4.14 (2H, bs),  
10 4.21 (2H, d,  $J=5.8$  Hz), 4.58 (1H, bs), 5.95 (1H, s),  
7.27-7.31 (2H, m), 7.42 (1H, d,  $J=1.6$  Hz), 7.48-7.59 (3H, m),  
7.91 (1H, dd,  $J=1.6, 8.2$  Hz), 8.47 (1H, d,  $J=8.2$  Hz).

(3) Tert-butyl [6-(4-amino-1,3-thiazol-2-yl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-  
15 isoquinolinyl]methylcarbamate (0.14 g, 0.5 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 1 h. The reaction was concentrated under reduced pressure, and the residue was crystallized  
20 from ethyl acetate to give 3-(aminomethyl)-6-(4-amino-1,3-thiazol-2-yl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone dihydrochloride (0.13 g, 92.9%) as crystals.

Melting point 230°C.

25  $^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.94 (6H, d,  $J=6.2$  Hz), 1.99-2.21 (1H, m), 3.87 (2H, s), 4.10 (2H, d,  $J=8.2$  Hz), 5.48 (3H, bs), 7.10 (1H, s), 7.16-7.62 (6H, m), 8.03 (1H, d,  $J=8.4$  Hz), 8.44 (1H, d,  $J=8.4$  Hz), 8.67 (3H, bs).

#### Example 223

30 N-{2-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazol-4-yl}acetamide hydrochloride

(1) A solution of tert-butyl [6-(4-amino-1,3-thiazol-2-yl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-

35 isoquinolinyl]methylcarbamate (0.20 g, 0.4 mmol) and acetyl chloride (0.04 ml, 0.6 mmol) in N,N-

dimethylacetamide (10 ml) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl {6-[4-(acetylamino)-1,3-thiazol-2-yl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.18 g, 85.7%) as crystals.

Melting point 227-228°C.

Elemental analysis for  $C_{30}H_{34}N_4O_4S$

Calculated: C, 65.91; H, 6.27; N, 10.25.

Found: C, 65.66; H, 6.44; N, 10.17.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (6H, d,  $J=6.6$  Hz), 1.47 (9H, s), 2.18-2.39 (4H, m), 4.10 (2H, bs), 4.19 (2H, bs), 7.06-7.38 (4H, m), 7.41-7.56 (3H, m), 7.61 (1H, s), 8.13 (1H, bs), 8.69 (1H, bs).

(2) Tert-butyl {6-[4-(acetylamino)-1,3-thiazol-2-yl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.14 g, 0.25 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 1 h. The reaction was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate to give N-{2-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1,3-thiazol-4-yl}acetamide hydrochloride (0.11 g, 91.7%) as crystals.

Melting point 242-244°C.

Elemental analysis for  $C_{25}H_{27}N_4O_2ClS \cdot 2H_2O$

Calculated: C, 57.85; H, 6.02; N, 10.79.

Found: C, 57.70; H, 5.69; N, 10.69.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.93 (6H, d,  $J=6.6$  Hz), 1.99-2.18 (4H, m), 3.86 (2H, s), 4.10 (2H, d,  $J=6.3$  Hz), 7.45-7.48 (3H, m), 7.54-7.66 (4H, m), 8.05 (1H, d,  $J=8.6$  Hz), 8.46 (1H,

d,  $J=8.6$  Hz), 8.65 (3H, bs), 11.03 (1H, s).

**Example 224**

Methyl 2-([3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]oxy)-2-methylpropanoate

**5 hydrochloride**

(1) To a solution of tert-butyl [6-hydroxy-2-isobutyl-4-phenyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.42 g, 1 mmol) in N,N-dimethylformamide (10 ml) was added sodium hydride (48 mg, 1.2 mmol) (60% in oil). The  
10 resulting mixture was stirred at 0°C for 10 min. To the mixture was added methyl 2-bromoisobutyrate (0.22 g, 1.2 mmol), and the mixture was stirred at room temperature for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed  
15 with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give methyl 2-([3-([tert-butoxycarbonyl]amino)methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-  
20 isoquinolinyl]oxy)-2-methylpropanoate (0.31 g, 59.6%) as crystals.

Melting point 207-209°C.

Elemental analysis for  $C_{30}H_{38}N_2O_6 \cdot 0.25H_2O$

Calculated: C, 68.35; H, 7.36; N, 5.31.

25 Found: C, 68.39; H, 7.54; N, 5.31.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (6H, d,  $J=6.6$  Hz), 1.42 (9H, s), 1.51 (6H, s), 2.11-2.31 (1H, m), 3.53 (3H, s), 4.04 (2H, d,  $J=7.4$  Hz), 4.18 (2H, d,  $J=5.4$  Hz), 4.42 (1H, bs), 6.14 (1H, d,  $J=2.5$  Hz), 6.94 (1H, dd,  $J=2.5, 8.8$  Hz),  
30 7.19-7.24 (2H, m), 7.46-7.57 (3H, m), 8.35 (1H, d,  $J=8.8$  Hz).

(2) Methyl 2-([3-([tert-butoxycarbonyl]amino)methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]oxy)-2-methylpropanoate (0.16 g, 0.3 mmol)  
35 was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room

temperature for 1 h. The reaction was concentrated under reduced pressure, and the precipitated crystals were recrystallized from ethyl acetate - diisopropyl ether to give methyl 2-[[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]oxy]-2-methylpropanoate hydrochloride (0.10 g, 71.4%) as crystals.

Melting point 236-237°C.

Elemental analysis for  $C_{25}H_{31}N_2O_4Cl \cdot 1.25H_2O$

10 Calculated: C, 62.36; H, 7.01; N, 5.82.

Found: C, 62.32; H, 6.73; N, 5.58.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.91 (6H, d,  $J=6.6$  Hz), 1.44 (6H, s), 1.99-2.18 (1H, m), 3.45 (3H, s), 3.84 (2H, s), 4.05 (2H, d,  $J=7.0$  Hz), 5.99 (1H, d,  $J=2.4$  Hz), 7.02 (1H, dd,  $J=2.4, 8.8$  Hz), 7.34-7.39 (2H, m), 7.55-7.62 (3H, m), 8.23 (1H, d,  $J=8.8$  Hz), 8.57 (3H, bs).

#### Example 225

2-[[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]oxy]-2-methylpropanoic acid hydrochloride

(1) To a solution of methyl 2-[[3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]oxy]-2-methylpropanoate (0.37 g, 0.7 mmol) in tetrahydrofuran (10 ml) and methanol (10 ml) was added 1N sodium hydroxide solution (2 ml). The mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting crystals were crystallized from ethyl acetate - diisopropyl ether to give 2-[[3-[(tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]oxy]-2-methylpropanoic acid (0.32 g, 91.4%) as crystals.

Melting point 219-220°C.

Elemental analysis for  $C_{29}H_{36}N_2O_6$

Calculated: C, 68.48; H, 7.13; N, 5.51.

Found: C, 68.48; H, 7.19; N, 5.28.

5  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.98 (6H, d,  $J=6.6$  Hz), 1.42 (9H, s),  
1.59 (6H, s), 2.16-2.32 (1H, m), 4.07 (2H, d,  $J=7.4$  Hz),  
4.19 (2H, d,  $J=5.2$  Hz), 4.58 (1H, bs), 6.41 (1H, d,  
 $J=2.4$  Hz), 6.97 (1H, dd,  $J=2.4, 8.8$  Hz), 7.14-7.22 (2H,  
m), 7.41-7.56 (3H, m), 8.30 (1H, d,  $J=8.8$  Hz).

10 (2) 2-[(3-[(Tert-butoxycarbonyl)amino]methyl)-2-  
isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-  
isoquinolinyl]oxy]-2-methylpropanoic acid (0.13 g, 0.25  
mmol) was dissolved in a solution of 4N hydrogen  
chloride in ethyl acetate (5 ml). The solution was

15 stirred at room temperature for 1 h. The reaction  
mixture was concentrated under reduced pressure, and the  
residue was crystallized from ethyl acetate to give 2-  
{[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-  
6-isoquinolinyl]oxy}-2-methylpropanoic acid

20 hydrochloride (0.10 g, 90.9%) as crystals.

Melting point 256-257°C.

Elemental analysis for  $C_{24}H_{29}N_2O_4Cl \cdot 0.5H_2O$

Calculated: C, 63.50; H, 6.66; N, 6.17.

Found: C, 63.25; H, 6.66; N, 5.86.

25  $^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.91 (6H, d,  $J=6.6$  Hz), 1.44 (6H, s),  
1.99-2.14 (1H, m), 3.86 (2H, s), 4.03 (2H, d,  $J=6.9$  Hz),  
6.17 (1H, d,  $J=2.2$  Hz), 7.01 (1H, dd,  $J=2.2, 8.7$  Hz),  
7.34-7.37 (2H, m), 7.49-7.58 (3H, m), 8.22 (1H, d,  $J=8.7$   
Hz), 8.49 (3H, bs).

30 **Example 226**

2-[(3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-  
dihydro-6-isoquinolinyl]oxy]-2-methylpropanamide  
hydrochloride

(1) A solution of 2-[(3-[(tert-  
35 butoxycarbonyl)amino]methyl)-2-isobutyl-1-oxo-4-phenyl-  
1,2-dihydro-6-isoquinolinyl]oxy]-2-methylpropanoic acid

- (0.20 g, 0.4 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.15 g, 0.8 mmol) and 1-hydroxybenzotriazole ammonium salt (0.12 g, 0.8 mmol) in N,N-dimethylformamide (10 ml) was  
5 stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting crystals were  
10 recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl [6-(2-amino-1,1-dimethyl-2-oxoethoxy)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinoliny]methylcarbamate (0.19 g, 95.0%) as crystals.
- 15 Melting point 219-220°C.  
Elemental analysis for  $C_{29}H_{37}N_3O_5 \cdot 0.25H_2O$   
Calculated: C, 68.01; H, 7.38; N, 8.21.  
Found: C, 68.04; H, 7.46; N, 7.97.  
 $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.00 (6H, d,  $J=6.4$  Hz), 1.42 (9H, s),  
20 1.46 (6H, s), 2.12-2.31 (1H, m), 4.05 (2H, d,  $J=7.2$  Hz), 4.20 (2H, d,  $J=5.4$  Hz), 4.45 (1H, bs), 5.36 (1H, bs), 6.34 (1H, bs), 6.39 (1H, d,  $J=2.6$  Hz), 7.03 (1H, dd,  $J=2.6, 8.8$  Hz), 7.20-7.25 (2H, m), 7.48-7.58 (3H, m), 8.39 (1H, d,  $J=8.8$  Hz).
- 25 (2). Tert-butyl [6-(2-amino-1,1-dimethyl-2-oxoethoxy)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinoliny]methylcarbamate (0.15 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room  
30 temperature for 1 h. The reaction was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate to give 2-[[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyloxy]-2-methylpropanamide hydrochloride  
35 (0.12 g, 92.3%) crystals.  
Melting point 182-184°C.

Elemental analysis for  $C_{24}H_{30}N_3O_3Cl$  AcOEt

Calculated: C, 63.21; H, 7.20; N, 7.90.

Found: C, 63.31; H, 7.47; N, 8.11.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.91 (6H, d,  $J=6.6$  Hz), 1.38 (6H, s),  
5 1.99-2.18 (1H, m), 3.85 (2H, s), 4.04 (2H, d,  $J=6.8$  Hz),  
6.27 (1H, d,  $J=2.2$  Hz), 7.04 (1H, dd,  $J=2.2, 8.8$  Hz),  
7.17 (1H, bs), 7.34-7.38 (2H, m), 7.44 (1H, bs), 7.54-  
7.61 (3H, m), 8.22 (1H, d,  $J=8.8$  Hz), 8.55 (3H, bs).

#### Example 227

10 6-Acetyl-3-(aminomethyl)-4-butoxy-2-isobutyl-1(2H)-  
isoquinolinone hydrochloride  
(1) A solution of 4-butoxy-3-[(tert-  
butoxycarbonyl)amino]methyl)-2-isobutyl-1-oxo-1,2-  
dihydro-6-isoquinolinecarboxylic acid (4.46 g, 10 mmol),  
15 N,O-dimethylhydroxyamine hydrochloride (1.17 g, 12 mmol),  
1-ethyl-3-(3-dimethylaminopropyl)carbodiimide  
hydrochloride (2.30 g, 12 mmol), 1-hydroxybenzotriazole  
(1.84 g, 12 mmol) and triethylamine (1.7 ml, 12 mmol) in  
N,N-dimethylformamide (10 ml) was stirred at room  
20 temperature for 2 h. The reaction mixture was poured  
into water and extracted with ethyl acetate. The extract  
was washed with brine, dried over anhydrous magnesium  
sulfate and concentrated under reduced pressure. The  
resulting crystals were recrystallized from ethyl  
25 acetate - diisopropyl ether to give tert-butyl (4-  
butoxy-2-isobutyl-6-[(methoxy(methyl)amino]carbonyl)-1-  
oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (4.15 g,  
84.9%) as crystals.

Melting point 142-143°C.

30 Elemental analysis for  $C_{26}H_{39}N_3O_6$

Calculated: C, 63.78; H, 8.03; N, 8.58.

Found: C, 63.59; H, 8.10; N, 8.58.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.97 (6H, d,  $J=6.9$  Hz), 1.02 (3H, t,  
 $J=7.0$  Hz), 1.47 (9H, s), 1.48-1.62 (2H, m), 1.79-1.93  
35 (2H, m), 2.12-2.26 (1H, m), 3.41 (3H, s), 3.54 (3H, s),  
3.88 (2H, t,  $J=6.5$  Hz), 4.01 (2H, d,  $J=7.6$  Hz), 4.53 (2H,



d, J=5.6 Hz), 4.74 (1H, bs), 7.74 (1H, dd, J=1.4, 8.6 Hz), 7.99 (1H, d, J=1.4 Hz), 8.46 (1H, d, J=8.6 Hz).

- (2) To a solution of tert-butyl (4-butoxy-2-isobutyl-6-  
5 {methoxy(methyl)amino}carbonyl)-1-oxo-1,2-dihydro-3-  
isoquinolinyl)methylcarbamate (0.49 g, 1 mmol) in  
tetrahydrofuran (10 ml) was added 1N methylmagnesium  
bromide tetrahydrofuran solution (5 ml) at 0°C. The  
mixture was stirred at 0°C for 1 h. The reaction mixture  
was poured into water and extracted with ethyl acetate.  
10 The extract was washed with brine, dried over anhydrous  
magnesium sulfate and concentrated under reduced  
pressure. The residue was purified by silica gel column  
chromatography to give tert-butyl (6-acetyl-4-butoxy-2-  
isobutyl-1-oxo-1,2-dihydro-3-  
15 isoquinolinyl)methylcarbamate (0.37 g, 84.1%) as  
crystals.

Melting point 161-162°C.

Elemental analysis for  $C_{25}H_{36}N_2O_5$

Calculated: C, 67.54; H, 8.16; N, 6.30.

- 20 Found: C, 67.30; H, 8.14; N, 6.21.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.97 (6H, d, J=6.6 Hz), 1.06 (3H, t,  
J=7.2 Hz), 1.47 (9H, s), 1.53-1.72 (2H, m), 1.82-1.97  
(2H, m), 2.12-2.25 (1H, m), 2.71 (3H, s), 3.90 (2H, t,  
J=6.5 Hz), 4.01 (2H, d, J=7.4 Hz), 4.54 (2H, d, J=5.6  
25 Hz), 4.78 (1H, bs), 8.01 (1H, dd, J=2.0, 8.4 Hz), 8.28  
(1H, d, J=2.0 Hz), 8.49 (1H, d, J=8.4 Hz).

- (3) Tert-butyl (6-acetyl-4-butoxy-2-isobutyl-1-oxo-1,2-  
dihydro-3-isoquinolinyl)methylcarbamate (0.13 g, 0.3  
mmol) was dissolved in a solution of 4N hydrogen  
30 chloride in ethyl acetate (5 ml). The solution was  
stirred at room temperature for 1 h. The reaction was  
concentrated under reduced pressure, and the  
precipitated crystals were recrystallized from methanol  
- diisopropyl ether to give 6-acetyl-3-(aminomethyl)-4-  
35 butoxy-2-isobutyl-1(2H)-isoquinolinone hydrochloride  
(0.10 g, 90.9%) as crystals.

Melting point 171.5-173°C.

Elemental analysis for  $C_{20}H_{29}N_2O_3Cl$

Calculated: C, 63.06; H, 7.67; N, 7.35.

Found: C, 62.77; H, 7.77; N, 7.26.

5  $^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.89 (6H, d,  $J=6.6$  Hz), 1.02 (3H, t,  $J=7.4$  Hz), 1.52-1.70 (2H, m), 1.84-2.16 (3H, m), 2.72 (3H, s), 3.92-4.01 (4H, m), 4.20 (2H, s), 8.12 (1H, d,  $J=8.2$  Hz), 8.26 (1H, s), 8.39 (1H, d,  $J=8.2$  Hz), 8.70 (3H, bs).

10 The compounds of following Examples 228 to 252 were synthesized according to the method similar to that in Example 214 (2) from the N-Boc intermediates.

**Example 228**

(E)-3-[3-(Aminomethyl)-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenoic acid hydrochloride

Melting point 268-270°C.

Elemental analysis for  $C_{23}H_{24}N_2O_3Cl_2 \cdot 0.5H_2O$

Calculated: C, 60.53; H, 5.52; N, 6.14.

20 Found: C, 60.49; H, 5.75; N, 5.81.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.92 (6H, d,  $J=6.6$  Hz), 2.04-2.18 (1H, m), 3.86 (2H, s), 4.07 (2H, d,  $J=6.6$  Hz), 6.52 (1H, d,  $J=15.9$  Hz), 7.09 (1H, s), 7.44 (2H, d,  $J=8.1$  Hz), 7.56 (1H, d,  $J=15.9$  Hz), 7.64 (2H, d,  $J=8.1$  Hz), 7.96 (1H, d,  $J=8.7$  Hz), 8.33 (1H, d,  $J=8.7$  Hz), 8.53 (3H, bs).

**Example 229**

Methyl 3-(aminomethyl)-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylate hydrochloride  
Melting point 177-179°C.

30 Elemental analysis for  $C_{22}H_{24}N_2O_3Cl_2 \cdot 0.25H_2O$

Calculated: C, 60.07; H, 5.61; N, 6.37.

Found: C, 60.00; H, 5.89; N, 6.24.

35  $^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.93 (6H, d,  $J=6.6$  Hz), 2.02-2.18 (1H, m), 3.82 (3H, s), 3.88 (2H, s), 4.08 (2H, d,  $J=7.0$  Hz), 7.46 (2H, d,  $J=8.4$  Hz), 7.61 (1H, d,  $J=1.6$  Hz), 7.68 (2H, d,  $J=8.4$  Hz), 8.08 (1H, dd,  $J=1.6, 8.4$  Hz), 8.46 (1H, d,

J=8.4 Hz), 8.52 (3H, bs).

**Example 230**

3-(Aminomethyl)-4-(4-chlorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid hydrochloride

5 Melting point 263-265°C.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.93 (6H, d, J=6.6 Hz), 1.99-2.18 (1H, m), 3.88 (2H, s), 4.08 (2H, d, J=7.0 Hz), 7.46 (2H, d, J=8.4 Hz), 7.51 (1H, d, J=1.4 Hz), 7.67 (2H, d, J=8.4 Hz), 8.06 (1H, dd, J=1.4, 8.2 Hz), 8.44 (1H, d, J=8.2 Hz), 8.46 (3H, bs).

**Example 231**

3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarbothioamide hydrochloride

Melting point 257-259°C.

15 Elemental analysis for C<sub>21</sub>H<sub>24</sub>N<sub>3</sub>OClS 0.5H<sub>2</sub>O

Calculated: C, 61.37; H, 6.13; N, 10.22.

Found: C, 61.04; H, 5.99; N, 9.85.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.92 (6H, d, J=6.6 Hz), 1.99-2.18 (1H, m), 3.88 (2H, s), 4.06 (2H, d, J=7.2 Hz), 7.37-7.43 (3H, m), 7.56-7.59 (3H, m), 7.85 (1H, dd, J=1.5, 8.4 Hz), 8.32 (1H, d, J=8.4 Hz), 8.52 (3H, bs), 9.67 (1H, bs), 10.02 (1H, bs).

**Example 232**

3-(Aminomethyl)-6-(benzyloxy)-4-(4-chlorophenyl)-2-isobutyl-1(2H)-isoquinolinone hydrochloride

Melting point 162-164°C.

Elemental analysis for C<sub>27</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>Cl<sub>2</sub> 0.25H<sub>2</sub>O

Calculated: C, 66.46; H, 5.89; N, 5.74.

Found: C, 66.26; H, 5.87; N, 5.49.

30 <sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.90 (6H, d, J=6.6 Hz), 1.98-2.13 (1H, m), 3.82 (2H, s), 4.03 (2H, d, J=7.0 Hz), 5.04 (2H, s), 6.26 (1H, d, J=2.6 Hz), 7.23-7.59 (8H, m), 7.61 (2H, d, J=8.4 Hz), 8.25 (1H, d, J=8.8 Hz), 8.52 (3H, bs).

**Example 233**

35 3-(Aminomethyl)-4-(4-chlorophenyl)-6-hydroxy-2-isobutyl-1(2H)-isoquinolinone hydrochloride

Melting point 247-249°C.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.90 (6H, d, J=7.0 Hz), 1.99-2.13 (1H, m), 3.82 (2H, s), 3.99 (2H, d, J=7.4 Hz), 6.19 (1H, d, J=2.2 Hz), 6.99 (1H, dd, J=2.2, 8.8 Hz), 7.40 (2H, d, J=8.4 Hz), 7.63 (2H, d, J=8.4 Hz), 8.16 (1H, d, J=8.8 Hz), 8.42 (3H, bs), 10.30 (1H, s).

**Example 234**

(E)-3-[3-(Aminomethyl)-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenoic acid

10 hydrochloride

Melting point 230-231°C.

Elemental analysis for C<sub>25</sub>H<sub>27</sub>N<sub>2</sub>O<sub>3</sub>Cl H<sub>2</sub>O

Calculated: C, 64.78; H, 6.57; N, 6.30.

Found: C, 64.73; H, 6.63; N, 5.86.

15 <sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.92 (6H, d, J=6.6 Hz), 2.06-2.18 (1H, m), 2.45 (3H, s), 3.89 (2H, s), 4.07 (2H, d, J=6.6 Hz), 6.47 (1H, d, J=16.0 Hz), 7.05 (1H, d, J=1.2 Hz), 7.29 (2H, d, J=8.1 Hz), 7.40 (2H, d, J=8.1 Hz), 7.49 (1H, d, J=16.0 Hz), 7.94 (1H, dd, J=1.2, 8.1 Hz), 8.33 (1H, d, J=8.1 Hz), 8.50 (3H, bs).

**Example 235**

Methyl 3-(aminomethyl)-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinecarboxylate hydrochloride

Melting point 254-256°C.

25 Elemental analysis for C<sub>23</sub>H<sub>27</sub>N<sub>2</sub>O<sub>3</sub>Cl 0.25H<sub>2</sub>O

Calculated: C, 65.86; H, 6.61; N, 6.68.

Found: C, 66.03; H, 6.67; N, 6.50.

30 <sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.92 (6H, d, J=6.6 Hz), 2.06-2.16 (1H, m), 2.45 (3H, s), 3.81 (3H, s), 3.89 (2H, s), 4.10 (2H, d, J=6.9 Hz), 7.31 (2H, d, J=7.8 Hz), 7.41 (2H, d, J=7.8 Hz), 7.57 (1H, s), 8.06 (1H, d, J=8.3 Hz), 8.45 (1H, d, J=8.3 Hz), 8.57 (3H, bs).

**Example 236**

3-(Aminomethyl)-2-isobutyl-4-(4-methylphenyl)-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid hydrochloride

Melting point 259-261°C.

Elemental analysis for  $C_{22}H_{25}N_2O_3Cl \cdot 0.75H_2O$

Calculated: C, 63.76; H, 6.45; N, 6.76.

Found: C, 63.66; H, 6.49; N, 6.50.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.92 (6H, d,  $J=6.6$  Hz), 1.99-2.14 (1H, m), 2.45 (3H, s), 3.89 (2H, s), 4.09 (2H, d,  $J=7.4$  Hz), 7.31 (2H, d,  $J=7.9$  Hz), 7.42 (2H, d,  $J=7.9$  Hz), 7.57 (1H, d,  $J=1.4$  Hz), 8.05 (1H, dd,  $J=1.4, 8.4$  Hz), 8.43 (1H, d,  $J=8.4$  Hz), 8.53 (3H, bs).

**Example 237**

10 3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarbothioamide hydrochloride

Melting point 200-202°C.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.88 (6H, d,  $J=6.6$  Hz), 1.00 (3H, t,  $J=7.3$  Hz), 1.49-1.67 (2H, m), 1.79-2.08 (3H, m), 3.95-4.01 (4H, m), 4.19 (2H, bs), 7.98 (1H, dd,  $J=1.5, 8.5$  Hz), 8.20 (1H, d,  $J=1.5$  Hz), 8.28 (1H, d,  $J=8.5$  Hz), 8.51 (3H, bs), 9.87 (1H, bs), 10.20 (3H, bs).

**Example 238**

20 3-(Aminomethyl)-6-(benzyloxy)-2-isobutyl-4-(4-methylphenyl)-1(2H)-isoquinolinone hydrochloride

Melting point 244-246°C.

Elemental analysis for  $C_{28}H_{31}N_2O_2Cl$

Calculated: C, 72.63; H, 6.75; N, 6.05.

Found: C, 72.31; H, 6.84; N, 5.93.

25  $^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.89 (6H, d,  $J=6.6$  Hz), 1.98-2.18 (1H, m), 2.43 (3H, s), 3.84 (2H, s), 4.02 (2H, d,  $J=7.4$  Hz), 5.01 (2H, s), 6.31 (1H, d,  $J=2.2$  Hz), 7.18-7.38 (10H, m), 8.24 (1H, d,  $J=8.8$  Hz), 8.45 (3H, bs).

**Example 239**

30 3-(Aminomethyl)-6-hydroxy-2-isobutyl-4-(4-methylphenyl)-1(2H)-isoquinolinone hydrochloride

Melting point 255-256°C.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.90 (6H, d,  $J=7.0$  Hz), 1.99-2.13 (1H, m), 2.42 (3H, s), 3.83 (2H, s), 4.02 (2H, d,  $J=7.4$  Hz), 6.23 (1H, d,  $J=2.4$  Hz), 6.99 (1H, d,  $J=2.4, 8.6$  Hz), 7.25 (2H, d,  $J=8.1$  Hz), 7.37 (2H, d,  $J=8.1$  Hz), 8.15 (1H,

d, J=8.6 Hz), 8.50 (3H, bs), 10.27 (1H, s).

**Example 240**

(E)-3-[3-(Aminomethyl)-4-(4-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]-2-propenoic acid

5 hydrochloride

Melting point 255-256°C.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.93 (6H, d, J=6.6 Hz), 1.99-2.18 (1H, m), 3.87 (2H, s), 4.08 (2H, d, J=7.0 Hz), 6.50 (1H, d, J=16.2 Hz), 7.07 (1H, d, J=1.2 Hz), 7.36-7.48 (4H, m),  
10 7.55 (1H, d, J=16.2 Hz), 7.95 (1H, dd, J=1.2, 8.0 Hz), 8.33 (1H, d, J=8.0 Hz), 8.59 (3H, bs).

**Example 241**

3-(Aminomethyl)-6-(benzyloxy)-4-(4-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone hydrochloride

15 Melting point 226-227°C.

Elemental analysis for C<sub>27</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>ClF

Calculated: C, 69.44; H, 6.04; N, 6.00.

Found: C, 69.44; H, 5.89; N, 6.12.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.90 (6H, d, J=6.6 Hz), 1.99-2.14 (1H, m), 3.83 (2H, s), 4.04 (2H, d, J=7.4 Hz), 5.04 (2H, s),  
20 6.26 (1H, d, J=2.6 Hz), 7.23-7.44 (10H, m), 8.25 (1H, d, J=8.8 Hz), 8.56 (3H, bs).

**Example 242**

3-(Aminomethyl)-4-(4-fluorophenyl)-6-hydroxy-2-isobutyl-1(2H)-isoquinolinone hydrochloride

25

Melting point 249-251°C.

Elemental analysis for C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>ClF 1.5H<sub>2</sub>O

Calculated: C, 59.48; H, 6.24; N, 6.94.

Found: C, 59.21; H, 5.99; N, 6.68.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.91 (6H, d, J=6.6 Hz), 1.98-2.16 (1H, m), 3.82 (2H, d, J=7.0 Hz), 4.03 (2H, d, J=7.0 Hz), 6.19 (1H, d, J=2.2 Hz), 6.98 (1H, bs), 7.01 (1H, d, J=2.2, 8.8 Hz), 7.34-7.48 (4H, m), 8.16 (1H, d, J=8.8 Hz), 8.61 (3H, bs).

35 **Example 243**

Methyl 3-(aminomethyl)-4-(3-fluorophenyl)-2-isobutyl-1-

oxo-1,2-dihydro-6-isoquinolinecarboxylate hydrochloride

Melting point 177-179°C.

Elemental analysis for  $C_{22}H_{24}N_2O_3ClF \cdot 0.5H_2O$

Calculated: C, 61.75; H, 5.89; N, 6.55.

5 Found: C, 61.55; H, 6.04; N, 6.34.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.93 (6H, d, J=6.6 Hz), 2.04-2.18 (1H, m), 3.81 (3H, s), 3.89 (2H, s), 3.89 (2H, d, J=7.8 Hz), 7.27-7.47 (3H, m), 7.51 (1H, d, J=1.3 Hz), 7.62-7.70 (1H, m), 8.08 (1H, dd, J=1.3, 8.4 Hz), 8.46 (1H, d, J=8.4 Hz),  
10 8.59-8.67 (3H, m).

**Example 244**

3-(Aminomethyl)-4-(3-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid hydrochloride

Melting point 252-254°C.

15 Elemental analysis for  $C_{21}H_{22}N_2O_3ClF \cdot 0.75H_2O$

Calculated: C, 60.29; H, 5.66; N, 6.70.

Found: C, 60.29; H, 5.97; N, 6.53.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.93 (6H, d, J=6.6 Hz), 1.99-2.18 (1H, m), 3.89 (2H, bs), 4.04-4.17 (2H, m), 7.27-7.52 (4H, m),  
20 7.60-7.71 (1H, m), 8.06 (1H, dd, J=1.2, 8.4 Hz), 8.44 (1H, d, J=8.4 Hz), 8.63 (3H, bs).

**Example 245**

3-(Aminomethyl)-6-(benzyloxy)-4-(3-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone hydrochloride

25 Melting point 178-180°C.

Elemental analysis for  $C_{27}H_{28}N_2O_2ClF \cdot 0.25H_2O$

Calculated: C, 68.78; H, 6.09; N, 5.94.

Found: C, 68.57; H, 6.20; N, 5.84.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.90 (6H, d, J=6.6 Hz), 1.99-2.11 (1H, m), 3.77-3.90 (2H, m), 3.96-4.13 (2H, m), 5.04 (2H, s),  
30 6.26 (1H, d, J=2.4 Hz), 7.16-7.43 (9H, m), 7.57-7.65 (1H, m), 8.25 (1H, d, J=8.7 Hz), 8.60 (3H, bs).

**Example 246**

3-(Aminomethyl)-4-(3-fluorophenyl)-6-hydroxy-2-isobutyl-1(2H)-isoquinolinone hydrochloride

35

Melting point 226-227°C.

Elemental analysis for  $C_{20}H_{22}N_2O_2ClF \cdot 1.5H_2O$

Calculated: C, 59.48; H, 6.24; N, 6.94.

Found: C, 59.28; H, 6.09; N, 6.85.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.91 (6H, d,  $J=6.6$  Hz), 1.98-2.12 (1H, m), 3.82 (2H, bs), 3.92-4.14 (2H, m), 6.20 (1H, d,  $J=2.4$  Hz), 7.02 (1H, d,  $J=2.4, 8.6$  Hz), 7.20-7.41 (3H, m), 7.56-7.67 (1H, m), 8.16 (1H, d,  $J=8.6$  Hz), 8.60 (3H, bs).

**Example 247**

10 Methyl {[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]oxy}acetate hydrochloride

Melting point 228-229°C.

Elemental analysis for  $C_{23}H_{27}N_2O_4Cl \cdot 0.25H_2O$

Calculated: C, 63.44; H, 6.37; N, 6.43.

15 Found: C, 63.53; H, 6.27; N, 6.30.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.91 (6H, d,  $J=6.6$  Hz), 1.99-2.18 (1H, m), 3.60 (3H, s), 3.86 (2H, s), 4.04 (2H, d,  $J=7.2$  Hz), 4.71 (2H, s), 6.13 (1H, d,  $J=2.4$  Hz), 7.20 (1H, dd,  $J=2.4, 8.8$  Hz), 7.34-7.39 (2H, m), 7.54-7.60 (3H, m), 8.26 (1H, d,  $J=8.8$  Hz), 8.47 (3H, bs).

**Example 248**

{[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]oxy}acetic acid hydrochloride

Melting point 255-257°C.

25 Elemental analysis for  $C_{22}H_{25}N_2O_4Cl \cdot 0.5H_2O$

Calculated: C, 62.04; H, 6.15; N, 6.58.

Found: C, 62.15; H, 6.28; N, 6.36.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.91 (6H, d,  $J=6.6$  Hz), 1.99-2.18 (1H, m), 3.86 (2H, s), 4.05 (2H, d,  $J=7.6$  Hz), 4.61 (2H, s), 6.20 (1H, d,  $J=2.2$  Hz), 7.18 (1H, dd,  $J=2.2, 8.8$  Hz), 7.35-7.40 (2H, m), 7.52-7.63 (3H, m), 8.26 (1H, d,  $J=8.8$  Hz), 8.55 (3H, bs).

**Example 249**

35 Methyl 3-(aminomethyl)-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylate hydrochloride

Melting point 243-245°C.



Elemental analysis for  $C_{22}H_{24}N_2O_3ClF \cdot 1.0H_2O$

Calculated: C, 63.23; H, 6.27; N, 6.70.

Found: C, 63.08; H, 5.89; N, 6.46.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.92 (3H, d,  $J=6.3$  Hz), 0.94 (3H, d,  $J=5.7$  Hz), 2.04-2.18 (1H, m), 3.77-3.80 (1H, m), 3.81 (3H, s), 3.97-4.05 (2H, m), 4.13-4.21 (1H, m), 7.44-7.58 (4H, m), 7.64-7.72 (1H, m), 8.10 (1H, dd,  $J=1.6, 8.7$  Hz), 8.48 (1H, d,  $J=8.7$  Hz), 8.66 (3H, bs).

**Example 250**

10 3-(Aminomethyl)-4-(2-fluorophenyl)-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid hydrochloride

Melting point 222-224°C.

Elemental analysis for  $C_{21}H_{22}N_2O_3ClF \cdot 0.75H_2O$

Calculated: C, 60.29; H, 5.66; N, 6.70.

15 Found: C, 60.37; H, 5.76; N, 6.31.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.92 (3H, d,  $J=6.6$  Hz), 0.94 (3H, d,  $J=6.6$  Hz), 2.05-2.17 (1H, m), 3.77-3.84 (1H, m), 3.95-4.22 (3H, m), 7.42-7.73 (5H, m), 8.08 (1H, dd,  $J=1.4, 8.2$  Hz), 8.45 (1H, d,  $J=8.2$  Hz), 8.66 (3H, bs).

20 **Example 251**

3-(Aminomethyl)-6-(benzyloxy)-4-(2-fluorophenyl)-2-isobutyl-1(2H)-isoquinolinone hydrochloride

Melting point 144-145°C.

Elemental analysis for  $C_{27}H_{28}N_2O_2ClF \cdot 0.5H_2O$

25 Calculated: C, 68.13; H, 6.14; N, 5.89.

Found: C, 68.08; H, 6.43; N, 5.83.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.89 (3H, d,  $J=6.6$  Hz), 0.91 (3H, d,  $J=6.6$  Hz), 1.99-2.16 (1H, m), 3.69-4.18 (4H, m), 5.04 (2H, s), 6.26 (1H, d,  $J=2.0$  Hz), 7.22-7.47 (9H, m), 7.59-7.68 (1H, m), 8.26 (1H, d,  $J=8.8$  Hz), 8.52 (3H, bs).

30 **Example 252**

3-(Aminomethyl)-4-(2-fluorophenyl)-6-hydroxy-2-isobutyl-1(2H)-isoquinolinone hydrochloride

Melting point 259-260°C.

35 Elemental analysis for  $C_{20}H_{22}N_2O_2Cl$

Calculated: C, 63.74; H, 5.88; N, 7.43.

Found: C, 63.38; H, 5.71; N, 7.43.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.89 (3H, d, J=6.6 Hz), 0.91 (3H, d, J=6.6 Hz), 2.01-2.18 (1H, m), 3.68-4.16 (4H, m), 6.20 (1H, d, J=2.4 Hz), 7.02 (1H, dd, J=2.4, 8.6 Hz), 7.37-7.67 (4H, m), 8.17 (1H, d, J=8.6 Hz), 8.55 (3H, bs), 10.37 (3H, bs).

**Example 253**

3-(Aminomethyl)-6-(benzyloxy)-2-isobutyl-4-(2-thienyl)-1(2H)-isoquinolinone hydrochloride

10 (1) A mixture of methyl 6-(benzyloxy)-2-isobutyl-1-oxo-4-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinecarboxylate (10.26 g, 20 mmol), 2-thiopheneboronic acid (3.07 g, 24 mmol), sodium carbonate (5.30 g, 50 mmol), toluene (50 ml), methanol  
15 (10 ml) and water (10 ml) was stirred at room temperature for 30 min under an argon atmosphere. To the resulting mixture was added tetrakis(triphenylphosphine)palladium (1.16 g, 1 mmol), the mixture was refluxed under heating for 10 h under an  
20 argon atmosphere. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography  
25 to give methyl 6-(benzyloxy)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinecarboxylate (2.11 g, 23.6%) as crystals.

Melting point 143-144°C.

Elemental analysis for C<sub>26</sub>H<sub>25</sub>NO<sub>4</sub>S

30 Calculated: C, 69.78; H, 5.63; N, 3.13.

Found: C, 69.77; H, 5.76; N, 3.15.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.92 (6H, d, J=7.0 Hz), 2.05-2.21 (1H, m), 3.59 (3H, s), 3.92 (2H, d, J=7.8 Hz), 5.02 (2H, s), 6.85 (1H, d, J=2.6 Hz), 6.98 (1H, dd, J=1.2, 3.4 Hz),  
35 7.10 (1H, dd, J=3.4, 5.1 Hz), 7.17 (1H, dd, J=2.4, 9.1 Hz), 7.29-7.42 (5H, m), 7.46 (1H, dd, J=1.2, 5.1 Hz),

8.39 (1H, d, J=9.1 Hz).

(2) To a suspension of methyl 6-(benzyloxy)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinecarboxylate (2.01 g, 4.5 mmol) in methanol (30 ml) was added a solution of lithium hydroxide monohydrate (0.57 g, 13.5 mmol) in water (10 ml). The resulting mixture was refluxed under heating for 48 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting crystals were recrystallized from ethyl acetate - n-hexane to give 6-(benzyloxy)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinecarboxylic acid (1.71 g, 87.7%) as crystals.

Melting point 171-172°C.

Elemental analysis for  $C_{25}H_{23}NO_4S \cdot 0.3H_2O$ :

Calculated: C, 68.41; H, 5.42; N, 3.19.

Found: C, 68.51; H, 5.84; N, 2.93.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.87 (6H, d, J=6.6 Hz), 2.13-2.26 (1H, m), 3.89 (2H, d, J=7.4 Hz), 5.00 (2H, s), 6.79 (1H, d, J=1.8 Hz), 7.08-7.13 (3H, m), 7.27-7.45 (5H, m), 7.46-7.48 (1H, m), 8.26 (1H, dd, J=1.4, 9.0 Hz).

(3) To a solution of 6-(benzyloxy)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinecarboxylic acid (1.52 g, 3.5 mmol) in tetrahydrofuran (20 ml) were added oxalyl chloride (0.37 ml, 4.2 mmol) and N,N-dimethylformamide (2 drops). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (10 ml). The solution was added dropwise to a suspension of sodium tetrahydroborate (0.47 g, 12.3 mmol) in 1,2-dimethoxyethane (20 ml) at 0°C, and the mixture was stirred at 0°C for 1 h. The reaction mixture was poured

into 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 6-(benzyloxy)-3-(hydroxymethyl)-2-isobutyl-4-(2-thienyl)-1(2H)-isoquinolinone (1.36 g, 92.5%) as crystals.

Elemental analysis for  $C_{25}H_{25}NO_3S$

Calculated: C, 71.57; H, 6.01; N, 3.34.

10 Found: C, 71.32; H, 6.08; N, 3.25.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.96 (6H, d,  $J=7.0$  Hz), 2.11-2.35 (1H, m), 4.18 (2H, d,  $J=7.4$  Hz), 4.53 (2H, d,  $J=6.2$  Hz), 4.94 (2H, s), 6.55 (1H, d,  $J=2.2$  Hz), 7.00-7.05 (2H, m), 7.18 (1H, dd,  $J=3.5, 5.2$  Hz), 7.23-7.38 (5H, m), 7.48 (1H, dd,  $J=1.0, 5.2$  Hz), 8.30 (1H, d,  $J=9.0$  Hz).

(4) To a suspension of 6-(benzyloxy)-3-(hydroxymethyl)-2-isobutyl-4-(2-thienyl)-1(2H)-isoquinolinone (1.26 g, 3 mmol) in toluene (20 ml) was added thionyl chloride (0.44 ml, 6 mmol). The resulting mixture was refluxed for 2 h. The reaction mixture was added to a saturated sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 6-(benzyloxy)-3-(chloromethyl)-2-isobutyl-4-(2-thienyl)-1(2H)-isoquinolinone (1.30 g, 100%) as an oil.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.00 (6H, d,  $J=6.6$  Hz), 2.12-2.31 (1H, m), 4.14 (2H, bs), 4.48 (2H, s), 4.99 (2H, s), 6.61 (1H, d,  $J=2.6$  Hz), 7.05 (1H, dd,  $J=1.6, 3.5$  Hz), 7.11-7.38 (7H, m), 7.51 (1H, dd,  $J=1.6, 5.1$  Hz), 8.38 (1H, d,  $J=8.8$  Hz).

(5) A solution of 6-(benzyloxy)-3-(chloromethyl)-2-isobutyl-4-(2-thienyl)-1(2H)-isoquinolinone (1.31 g, 3 mmol) and potassium phthalimide (0.83 g, 4.5 mmol) in  $N,N$ -dimethylformamide (20 ml) was stirred at room temperature for 3 h. The reaction mixture was poured

into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography  
5 to give 2-{{6-(benzyloxy)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione (1.42 g, 86.6%) as an amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.98 (6H, d, J=6.6 Hz), 2.12-2.25 (1H,  
10 m), 4.02 (1H, d, J=6.6 Hz), 4.87 (2H, d, J=3.2 Hz), 4.97 (2H, s), 6.55 (1H, d, J=2.2 Hz), 7.01 (1H, dd, J=1.3, 3.5 Hz), 7.08-7.14 (2H, m), 7.28-7.39 (5H, m), 7.43 (1H, dd, J=1.3, 5.3 Hz), 7.68-7.80 (4H, m), 8.36 (1H, d, J=9.2 Hz).

15 (6) To a suspension of 2-{{6-(benzyloxy)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinyl)methyl}-1H-isoindole-1,3(2H)-dione (1.37 g, 2.5 mmol) in ethanol (20 ml) was added hydrazine monohydrate (0.36 ml, 7.5 mmol). The mixture was refluxed for 1 h. The reaction  
20 mixture was poured into a saturated sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in  
25 tetrahydrofuran (20 ml), and then di-t-butyl dicarbonate (0.69 ml, 3 mmol) was added thereto. The resulting mixture was refluxed for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous  
30 magnesium sulfate and concentrated under reduced pressure. The resulting crystals were recrystallized from ethyl acetate - diisopropyl ether to give tert-butyl [6-(benzyloxy)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinyl)methylcarbamate (1.19 g, 92.2%)  
35 as crystals.

Melting point 176-177°C.

Elemental analysis for  $C_{30}H_{34}N_2O_4S$

Calculated: C, 69.47; H, 6.61; N, 5.40.

Found: C, 69.44; H, 6.68; N, 5.36.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.98 (6H, d,  $J=7.0$  Hz), 1.43 (9H, s),  
5 2.14-2.28 (1H, m), 4.05 (2H, bs), 4.30 (2H, d,  $J=5.0$  Hz),  
4.56 (1H, bs), 4.98 (2H, s), 6.55 (1H, d,  $J=2.6$  Hz),  
6.94 (1H, dd,  $J=1.2, 3.5$  Hz), 7.10 (1H, dd,  $J=2.6, 8.8$   
Hz), 7.17 (1H, dd,  $J=3.5, 5.4$  Hz), 7.26-7.39 (5H, m),  
7.48 (1H, dd,  $J=1.2, 5.4$  Hz), 8.35 (1H, d,  $J=8.8$  Hz).

10 (7) Tert-butyl [6-(benzyloxy)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate  
(0.15 g, 0.3 mmol) was dissolved in a solution of 4N  
hydrogen chloride in ethyl acetate (5 ml). The solution  
was stirred at room temperature for 1 h. The reaction  
15 mixture was concentrated under reduced pressure, and the  
precipitated crystals were recrystallized from ethyl  
acetate - diisopropyl ether to give 3-(aminomethyl)-6-  
(benzyloxy)-2-isobutyl-4-(2-thienyl)-1(2H)-  
isoquinolinone hydrochloride (0.11 g, 84.6%) as crystals.

20 Melting point 139-141°C.

Elemental analysis for  $C_{25}H_{27}N_2O_2ClS \cdot 0.5H_2O$

Calculated: C, 64.71; H, 6.08; N, 6.04.

Found: C, 65.01; H, 6.18; N, 5.74.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.89 (6H, d,  $J=6.6$  Hz), 1.99-2.09 (1H,  
25 m), 3.98 (2H, bs), 4.08 (2H, bs), 5.06 (2H, bs), 6.49 (1H,  
d,  $J=2.2$  Hz), 7.20-7.41 (8H, m), 7.85 (1H, dd,  $J=1.1,$   
5.1 Hz), 8.23 (1H, d,  $J=9.0$  Hz), 8.59 (3H, bs).

#### Example 254

3-(Aminomethyl)-6-hydroxy-2-isobutyl-4-(2-thienyl)-  
30 1(2H)-isoquinolinone hydrochloride

(1) A suspension of tert-butyl [6-(benzyloxy)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (1.04 g, 2 mmol) and 5%  
palladium carbon (1.0 g) in ethanol (10 ml) and  
35 tetrahydrofuran (10 ml) was stirred under a hydrogen  
atmosphere at room temperature for 2 h. The catalyst was

filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [6-hydroxy-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-

5 isoquinolinyl]methylcarbamate (0.82 g, 96.5%) as crystals.

Melting point 216-217°C.

Elemental analysis for  $C_{23}H_{28}N_2O_4S$

Calculated: C, 64.46; H, 6.59; N, 6.54.

10 Found: C, 64.38; H, 6.60; N, 6.33.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.97 (6H, d,  $J=6.6$  Hz), 1.43 (9H, s), 2.13-2.25 (1H, m), 4.04 (2H, bs), 4.30 (2H, d,  $J=5.2$  Hz), 4.57 (1H, bs), 6.53 (1H, d,  $J=2.4$  Hz), 6.97 (1H, d,  $J=2.8$  Hz), 7.03 (1H, dd,  $J=2.4, 8.8$  Hz), 7.13 (1H, dd,  $J=2.8, 5.6$  Hz), 7.40 (1H, bs), 7.42 (1H, d,  $J=5.6$  Hz), 8.28 (1H, d,  $J=8.8$  Hz).

(2) Tert-butyl [6-hydroxy-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.15 g, 0.35 mmol) was dissolved in a solution of 4N  
20 hydrogen chloride in ethyl acetate solution (5 ml). The solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduce pressure, and the residue was crystallized from ethyl acetate - diisopropyl ether to give 3-(aminomethyl)-6-hydroxy-2-isobutyl-4-(2-thienyl)-1(2H)-isoquinolinone  
25 hydrochloride (0.10 g, 83.3%) as crystals.

Melting point 249-251°C.

Elemental analysis for  $C_{18}H_{21}N_2O_2ClS \cdot H_2O$

Calculated: C, 56.46; H, 6.05; N, 7.32.

30 Found: C, 56.54; H, 6.35; N, 7.06.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.90 (6H, d,  $J=6.6$  Hz), 1.99-2.12 (1H, m), 3.98 (2H, bs), 4.08 (2H, bs), 6.41 (1H, d,  $J=2.3$  Hz), 7.03 (1H, dd,  $J=2.3, 8.6$  Hz), 7.06 (1H, bs), 7.26-7.29 (2H, m), 7.82 (1H, dd,  $J=2.8, 3.8$  Hz), 8.14 (1H, d,  $J=8.6$  Hz), 8.67 (3H, bs).

**Example 255**

2-([3-(Aminomethyl)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-6-isoquinolinyl]oxy)acetamide hydrochloride

- (1) A solution of tert-butyl [6-hydroxy-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.43 g, 1 mmol), and 2-iodoacetamide (0.37 g, 2 mmol) and 1,8-diazabicyclo[5.4.0]-7-undecene (0.30 ml, 2 mmol) in N,N-dimethylacetamide (10 ml) was stirred at 80°C for 10 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [6-(2-amino-2-oxoethoxy)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.19 g, 39.6%) as crystals.

Melting point 219-221°C.

Elemental analysis for  $C_{25}H_{31}N_3O_5S \cdot 0.25H_2O$

- 20 Calculated: C, 61.27; H, 6.48; N, 8.57.

Found: C, 61.02; H, 6.38; N, 8.37.

- $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (6H, d,  $J=6.6$  Hz), 1.44 (9H, s), 2.16-2.26 (1H, m), 4.07 (2H, bs), 4.31 (2H, d,  $J=6.0$  Hz), 4.39 (2H, s), 4.61 (1H, bs), 5.72 (1H, bs), 6.50 (1H, d,  $J=2.5$  Hz), 6.51 (1H, bs), 7.01 (1H, dd,  $J=1.2, 3.6$  Hz), 7.06 (1H, dd,  $J=2.5, 8.9$  Hz), 7.20 (1H, dd,  $J=3.6, 5.4$  Hz), 7.51 (1H, dd,  $J=1.2, 5.4$  Hz), 8.40 (1H, d,  $J=8.9$  Hz).

- (2) Tert-butyl [6-(2-amino-2-oxoethoxy)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.14 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 2 h. The reaction was concentrated under reduced pressure to give 2-([3-(aminomethyl)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-6-



isoquinolinyl]oxy}acetamide hydrochloride (0.11 g, 91.7%) as an amorphous solid.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.90 (6H, d, J=6.6 Hz), 1.99-2.14 (1H, m), 3.98-4.09 (4H, m), 4.41 (2H, s), 6.50 (1H, d, J=2.6 Hz), 7.21 (1H, dd, J=2.6, 9.0 Hz), 7.26-7.30 (2H, m), 7.35 (1H, bs), 7.60 (1H, bs), 7.83 (1H, dd, J=2.6, 4.0 Hz), 8.26 (1H, d, J=9.0 Hz), 8.63 (3H, s).

#### Example 256

Methyl 3-(aminomethyl)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-6-isoquinolinecarboxylate hydrochloride  
(1) To a solution of tert-butyl [6-hydroxy-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-

isoquinolinyl]methylcarbamate (1.07 g, 2.5 mmol) in N,N-dimethylformamide (10 ml) was added sodium hydride (0.12

g, 3 mmol)(60% in oil) at 0°C, and then the mixture was

stirred at 0°C for 30 min. To the mixture was added N-phenyltrifluoromethanesulfonimide (1.07 g, 3 mmol), and

the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water and

extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was

purified by silica gel column chromatography to give tert-butyl [2-isobutyl-1-oxo-4-(2-thienyl)-6-

trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinyl]methylcarbamate (1.40 g, 100%) as an oil.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.99 (6H, d, J=6.6 Hz), 1.44 (9H, s), 2.15-2.27 (1H, m), 4.11 (2H, bs), 4.35 (2H, d, J=5.2 Hz), 4.58 (1H, bs), 7.00-7.06 (2H, m), 7.20-7.45 (2H, m), 7.53 (1H, dd, J=1.2, 5.3 Hz), 8.52 (1H, d, J=8.4 Hz).

(2) A mixture of tert-butyl [2-isobutyl-1-oxo-4-(2-thienyl)-6-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinyl]methylcarbamate (1.40 g, 2.5 mmol), 1,1'-bis(diphenylphosphino)ferrocene (66 mg, 0.12 mmol), triethylamine (0.39 ml, 2.8 mmol) and palladium acetate (27 mg, 0.12 mmol) in tetrahydrofuran (20 ml) and

methanol (20 ml) was stirred at 100°C under a carbon monoxide atmosphere at 5 atm for 3 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give methyl 3-[[tert-butoxycarbonyl]amino]methyl}-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-6-isoquinolinecarboxylate (1.02 g, 87.2%) as crystals.

Melting point 170-171°C.

Elemental analysis for  $C_{25}H_{30}N_2O_5S$

Calculated: C, 63.81; H, 6.43; N, 5.95.

Found: C, 63.68; H, 6.68; N, 5.68.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.01 (6H, d,  $J=7.0$  Hz), 1.44 (9H, s), 2.17-2.31 (1H, m), 3.88 (3H, s), 4.10 (2H, d,  $J=7.4$  Hz), 4.34 (2H, d,  $J=5.8$  Hz), 4.64 (1H, bs), 7.05 (1H, dd,  $J=1.1, 3.4$  Hz), 7.21 (1H, dd,  $J=3.4, 5.2$  Hz), 7.52 (1H, dd,  $J=1.1, 5.2$  Hz), 7.82 (1H, d,  $J=1.3$  Hz), 8.04 (1H, dd,  $J=1.3, 8.4$  Hz), 8.48 (1H, dd,  $J=0.8, 8.4$  Hz).

(3) Methyl 3-[[tert-butoxycarbonyl]amino]methyl}-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-6-isoquinolinecarboxylate (0.14 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate - diisopropyl ether to give methyl 3-(aminomethyl)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-6-isoquinolinecarboxylate hydrochloride (0.11 g, 91.7%) as crystals.

Melting point 227-229°C.

Elemental analysis for  $C_{20}H_{23}N_2O_3ClS \cdot 0.25H_2O$

Calculated: C, 58.39; H, 5.76; N, 6.81.

Found: C, 58.28; H, 6.09; N, 6.41.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.92 (6H, d,  $J=6.6$  Hz), 1.99-2.18 (1H,

m), 3.35 (2H, s), 3.84 (3H, s), 4.03 (2H, bs), 7.29-7.33 (2H, m), 7.72 (1H, d, J=1.4 Hz), 7.88 (1H, dd, J=2.6, 4.0 Hz), 8.08 (1H, dd, J=1.4, 8.4 Hz), 8.44 (1H, d, J=8.4 Hz), 8.69 (3H, bs).

5 **Example 257**

3-(Aminomethyl)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-6-isoquinolinecarboxylic acid hydrochloride  
(1) To a solution of methyl 3-[[tert-

butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-(2-  
10 thienyl)-1,2-dihydro-6-isoquinolinecarboxylate (0.85 g, 1.8 mmol) in tetrahydrofuran (10 ml) and methanol (10 ml) was added 1N sodium hydroxide solution (4 ml). The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water, acidified  
15 with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting crystals were recrystallized from tetrahydrofuran - diisopropyl ether  
20 to give 3-[[tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-6-isoquinolinecarboxylic acid (0.79 g, 96.3%) as crystals. Melting point 224-226°C.

Elemental analysis for  $C_{24}H_{28}N_2O_5S$

25 Calculated: C, 63.14; H, 6.18; N, 6.14.

Found: C, 63.00; H, 6.04; N, 5.94.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (6H, d, J=6.6 Hz), 1.49 (9H, s),  
2.12-2.26 (1H, m), 4.05 (2H, d, J=6.4 Hz), 4.30 (2H, d, J=4.4 Hz), 5.61 (1H, bs), 7.09 (1H, d, J=3.5 Hz), 7.21  
30 (1H, dd, J=3.5, 5.2 Hz), 7.53 (1H, dd, J=0.9, 5.2 Hz), 7.65 (1H, s), 7.91 (1H, d, J=8.6 Hz), 8.36 (1H, d, J=8.6 Hz).

(2) 3-[[tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-6-isoquinolinecarboxylic  
35 acid (0.14 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The

solution was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate - diisopropyl ether to give 3-(aminomethyl)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-6-isoquinolinecarboxylic acid hydrochloride (0.10 g, 90.9%) as crystals.

Melting point 208-210°C.

Elemental analysis for  $C_{19}H_{21}N_2O_3ClS \cdot H_2O$

Calculated: C, 55.54; H, 5.64; N, 6.82.

10 Found: C, 55.37; H, 5.74; N, 6.60.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.92 (6H, d,  $J=6.8$  Hz), 1.99-2.19 (1H, m), 3.33 (2H, s), 4.04 (2H, s), 7.28-7.32 (2H, m), 7.72 (1H, d,  $J=1.4$  Hz), 7.86-7.89 (1H, m), 8.06 (1H, dd,  $J=1.7, 8.2$  Hz), 8.41 (1H, d,  $J=8.2$  Hz), 8.60 (3H, bs).

15 **Example 258**

3-(Aminomethyl)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-6-isoquinolinecarboxamide hydrochloride

(1) A solution of 3-[(tert-butoxycarbonyl)amino]methyl)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-6-isoquinolinecarboxylic acid (0.59 g, 1.3 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.50 g, 2.6 mmol) and 1-hydroxybenzotriazole ammonium salt (0.40 g, 2.6 mmol) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting crystals were recrystallized from tetrahydrofuran - diisopropyl ether to give tert-butyl [6-(aminocarbonyl)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.56 g, 94.9%) as crystals.

35 Melting point 248-250°C.

Elemental analysis for  $C_{24}H_{29}N_3O_4S$

Calculated: C, 63.27; H, 6.42; N, 9.22.

Found: C, 62.99; H, 6.62; N, 9.00.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.99 (6H, d, J=7.0 Hz), 1.46 (9H, s), 2.14-2.27 (1H, m), 4.08 (2H, d, J=7.4 Hz), 4.31 (2H, d, J=5.4 Hz), 5.01 (1H, bs), 6.23 (2H, bs), 7.06 (1H, d, J=2.6 Hz), 7.17 (1H, dd, J=2.6, 5.2 Hz), 7.48 (1H, d, J=5.2 Hz), 7.52 (1H, d, J=1.7 Hz), 7.73 (1H, dd, J=1.7, 8.4 Hz), 8.38 (1H, d, J=8.4 Hz).

(2) Tert-butyl [6-(aminocarbonyl)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.23 g, 0.5 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 1 h. The reaction was concentrated under reduced pressure, and the precipitated crystals were crystallized from methanol-diethyl ether to give 3-(aminomethyl)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-6-isoquinolinecarboxamide hydrochloride (0.18 g, 94.7%) as crystals.

Melting point 246-248°C.

Elemental analysis for C<sub>19</sub>H<sub>22</sub>N<sub>3</sub>O<sub>3</sub>ClS 0.75H<sub>2</sub>O

Calculated: C, 56.29; H, 5.84; N, 10.36.

Found: C, 56.19; H, 5.97; N, 10.22.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.92 (6H, d, J=6.6 Hz), 2.02-2.18 (1H, m), 3.43 (2H, bs), 4.02 (2H, bs), 7.29-7.33 (2H, m), 7.61-7.63 (2H, m), 7.84-7.87 (1H, m), 8.01 (1H, dd, J=1.5, 8.4 Hz), 8.19 (1H, bs), 8.35 (1H, d, J=8.4 Hz), 8.60 (3H, bs).

#### Example 259

3-(Aminomethyl)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-6-isoquinolinecarbonitrile hydrochloride

(1) A solution of tert-butyl [6-(aminocarbonyl)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.23 g, 0.5 mmol) and cyanuric chloride (0.28 g, 1.5 mmol) in N,N-dimethylformamide (10 mmol) was stirred at 0°C for 1 h. The reaction mixture was poured into water and extracted

with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [6-cyano-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.20 g, 95.2%) as crystals.

Melting point 189-190°C.

Elemental analysis for  $C_{24}H_{27}N_3O_3S$

10 Calculated: C, 65.88; H, 6.22; N, 9.60.

Found: C, 65.96; H, 6.14; N, 9.51.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.00 (6H, d,  $J=7.0$  Hz), 1.44 (9H, s), 2.14-2.31 (1H, m), 4.10 (2H, bs), 4.36 (2H, bs), 4.57 (1H, bs), 7.03 (1H, dd,  $J=1.2, 3.6$  Hz), 7.23 (1H, dd,  $J=3.6, 5.1$  Hz), 7.46 (1H, d,  $J=1.5$  Hz), 7.55 (1H, dd,  $J=1.2, 5.1$  Hz), 7.65 (1H, dd,  $J=1.5, 8.2$  Hz), 8.52 (1H, d,  $J=8.2$  Hz).

(2) Tert-butyl [6-cyano-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.17 g, 0.4 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 1 h. The reaction was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate - diisopropyl ether to give 3-(aminomethyl)-2-isobutyl-1-oxo-4-(2-thienyl)-1,2-dihydro-6-isoquinolinecarbonitrile hydrochloride (0.14 g, 93.3%) as crystals.

Melting point 202-203°C.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.92 (6H, d,  $J=6.6$  Hz), 2.06-2.16 (1H, m), 3.98-4.09 (4H, m), 7.29-7.33 (2H, m), 7.41 (1H, s), 7.87-7.91 (1H, m), 7.98 (1H, dd,  $J=1.1, 8.4$  Hz), 8.46 (1H, d,  $J=8.4$  Hz), 8.69 (3H, bs).

#### Example 260

3-(Aminomethyl)-4-butoxy-2-isobutyl-6-(2-pyridyl)-1(2H)-isoquinolinone dihydrochloride

(1) A solution of tert-butyl (6-bromo-4-butoxy-2-

isobutyl-1-oxo-1,2-dihydro-3-  
isoquinolinyl)methylcarbamate (0.48 g, 1 mmol), tri-n-  
butyl(2-pyridyl)tin (0.37 g, 1 mmol) and  
tetrakis(triphenylphosphine)palladium (58 mg, 0.05 mmol)  
5 in N,N-dimethylformamide (10 ml) was stirred at 100°C  
for 10 h. The reaction mixture was poured into water and  
extracted with ethyl acetate. The extract was washed  
with brine, dried over anhydrous magnesium sulfate and  
concentrated under reduced pressure. The residue was  
10 purified by silica gel column chromatography to give  
tert-butyl [4-butoxy-2-isobutyl-1-oxo-6-(2-pyridyl)-1,2-  
dihydro-3-isoquinolinyl)methylcarbamate (0.36 g, 75.0%)  
as crystals.

Melting point 123-124°C.

15 Elemental analysis for  $C_{28}H_{37}N_3O_4$

Calculated: C, 70.12; H, 7.78; N, 8.76.

Found: C, 69.91; H, 8.07; N, 8.71.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 0.98 (6H, d,  $J=6.6$  Hz), 1.05 (3H, t,  
 $J=7.3$  Hz), 1.47 (9H, s), 1.53-1.72 (2H, m), 1.84-1.97  
20 (2H, m), 2.05-2.27 (1H, m), 3.94 (2H, t,  $J=6.4$  Hz), 4.01  
(2H, d,  $J=7.8$  Hz), 4.55 (2H, d,  $J=5.4$  Hz), 4.82 (1H, bs),  
7.28-7.37 (1H, m), 7.77-7.85 (2H, m), 8.13 (1H, dd,  
 $J=1.8, 8.4$  Hz), 8.32 (1H, d,  $J=1.8$  Hz), 8.50 (1H, d,  
 $J=8.4$  Hz), 8.74-8.78 (1H, m).

25 (2) Tert-butyl [4-butoxy-2-isobutyl-1-oxo-6-(2-pyridyl)-  
1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.31 g,  
0.65 mmol) was dissolved in a solution of 4N hydrogen  
chloride in ethyl acetate (5 ml). The solution was  
stirred at room temperature for 2 h. The reaction was  
30 concentrated under reduced pressure to give 3-  
(aminomethyl)-4-butoxy-2-isobutyl-6-(2-pyridyl)-1(2H)-  
isoquinolinone dihydrochloride (0.27 g, 93.1%) as an  
amorphous solid.

Elemental analysis for  $C_{23}H_{31}N_3O_2Cl_2 \cdot H_2O$

35 Calculated: C, 58.72; H, 7.07; N, 8.93.

Found: C, 59.20; H, 7.46; N, 8.91.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.91 (6H, d, J=6.3 Hz), 1.01 (3H, t, J=7.2 Hz), 1.56-1.64 (2H, m), 1.87-1.95 (2H, m), 1.99-2.18 (1H, m), 4.02-4.06 (4H, m), 4.23 (2H, bs), 7.73 (1H, bs), 8.27-8.28 (3H, m), 8.42-8.44 (2H, m), 8.46 (4H, bs).

5 **Example 261**

3-(Aminomethyl)-4-butoxy-2-isobutyl-6-(2-thienyl)-1(2H)-isoquinolinone hydrochloride

- (1) A solution of tert-butyl (6-bromo-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.48 g, 1 mmol), tri-n-butyl(2-thienyl)tin (0.32 ml, 1 mmol) and tetrakis(triphenylphosphine)palladium (58 mg, 0.05 mmol) in tetrahydrofuran (20 ml) was refluxed for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [4-butoxy-2-isobutyl-1-oxo-6-(2-thienyl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.22 g, 45.8%) as crystals.

Melting point 130-131°C.

Elemental analysis for C<sub>27</sub>H<sub>36</sub>N<sub>2</sub>O<sub>4</sub>S

Calculated: C, 66.91; H, 7.49; N, 5.78.

- 25 Found: C, 66.85; H, 7.56; N, 5.70.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.97 (6H, d, J=6.6 Hz), 1.06 (3H, t, J=7.3 Hz), 1.47 (9H, s), 1.55-1.73 (2H, m), 1.83-1.97 (2H, m), 2.05-2.25 (1H, m), 3.91 (2H, t, J=6.4 Hz), 3.99 (2H, d, J=7.4 Hz), 4.53 (2H, d, J=5.6 Hz), 4.75 (1H, bs), 7.15 (1H, dd, J=3.6, 5.2 Hz), 7.39 (1H, dd, J=1.1, 5.2 Hz), 7.48 (1H, dd, J=1.1, 3.6 Hz), 7.75 (1H, dd, J=1.6, 8.4 Hz), 7.90 (1H, d, J=1.6 Hz), 8.40 (1H, d, J=8.4 Hz).

- (2) Tert-butyl [4-butoxy-2-isobutyl-1-oxo-6-(2-thienyl)-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.15 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was



stirred at room temperature for 2 h. The reaction was concentrated under reduced pressure, and the resulting crystals were recrystallized from methanol - diisopropyl ether to give 3-(aminomethyl)-4-butoxy-2-isobutyl-6-(2-thienyl)-1(2H)-isoquinolinone hydrochloride (0.11 g, 91.7%) as crystals.

Melting point 167-170°C.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.89 (6H, d, J=6.6 Hz), 1.03 (3H, t, J=7.3 Hz), 1.56-1.73 (2H, m), 1.82-2.11 (3H, m), 3.95-4.01 (4H, m), 4.20 (2H, s), 7.24 (1H, dd, J=3.7, 5.1 Hz), 7.72-7.76 (2H, m), 7.90 (1H, d, J=1.6 Hz), 7.96 (1H, dd, J=1.6, 8.4 Hz), 8.30 (1H, d, J=8.4 Hz), 8.64 (3H, bs).

#### Example 262

3-(Aminomethyl)-4-butoxy-6-(2-furyl)-2-isobutyl-1(2H)-isoquinolinone hydrochloride

(1) A solution of tert-butyl (6-bromo-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.48 g, 1 mmol), tri-n-butyl(2-furyl)tin (0.31 ml, 1 mmol) and tetrakis(triphenylphosphine)palladium (58 mg, 0.05 mmol) in tetrahydrofuran (20 ml) was refluxed at 80°C for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [4-butoxy-6-(2-furyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.35 g, 76.1%) as crystals.

Melting point 157-158°C.

Elemental analysis for C<sub>27</sub>H<sub>36</sub>N<sub>2</sub>O<sub>5</sub>

Calculated: C, 69.21; H, 7.74; N, 5.98.

Found: C, 68.88; H, 7.98; N, 5.75.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.97 (6H, d, J=6.6 Hz), 1.06 (3H, t, J=7.3 Hz), 1.47 (9H, s), 1.57-1.70 (2H, m), 1.86-1.95 (2H, m), 2.14-2.23 (1H, m), 3.91 (2H, t, J=6.6 Hz), 3.99

(2H, d, J=7.2 Hz), 4.53 (2H, d, J=5.7 Hz), 4.78 (1H, bs), 6.54 (1H, dd, J=1.5, 3.3 Hz), 6.85 (1H, dd, J=0.6, 3.3 Hz), 7.56 (1H, dd, J=0.6, 1.5 Hz), 7.76 (1H, dd, J=1.5, 8.4 Hz), 7.97 (1H, d, J=1.5 Hz), 8.40 (1H, d, J=8.4 Hz).

- 5 (2) Tert-butyl [4-butoxy-6-(2-furyl)-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.28 g, 0.6 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 2 h. The reaction was  
10 concentrated under reduced pressure, and the residue was crystallized from ethyl acetate - diisopropyl ether to give 3-(aminomethyl)-4-butoxy-6-(2-furyl)-2-isobutyl-1(2H)-isoquinolinone hydrochloride (0.22 g, 91.7%) as crystals.

- 15 Melting point 189-191°C.

Elemental analysis for  $C_{22}H_{29}N_2O_3Cl \cdot 1.75H_2O$

Calculated: C, 60.54; H, 7.51; N, 6.42.

Found: C, 60.46; H, 7.07; N, 6.33.

- $^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.88 (6H, d, J=6.6 Hz), 1.02 (3H, t, J=7.3 Hz), 1.51-1.69 (2H, m), 1.81-2.08 (3H, m), 3.93-3.99 (4H, m), 4.18 (2H, d, J=4.8 Hz), 6.99 (1H, dd, J=1.8, 3.3 Hz), 7.23 (1H, d, J=3.3 Hz), 7.90-7.97 (3H, m), 8.28 (1H, d, J=8.8 Hz), 8.75 (3H, bs).

#### Example 263

- 25 3-(Aminomethyl)-4-butoxy-2-isobutyl-6-phenyl-1(2H)-isoquinolinone hydrochloride

- (1) A mixture of tert-butyl (6-bromo-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.48 g, 1 mmol),  
30 phenylboric acid (0.15g, 1.2 mmol), sodium carbonate (0.26 g, 2.5 mmol), toluene (10 ml), ethanol (2 ml) and water (2 ml) was stirred at room temperature under an argon atmosphere for 30 min. To the resulting mixture was added tetrakis(triphenylphosphine)palladium (58 mg,  
35 0.05 mmol), and then the mixture was refluxed under an argon atmosphere for 10 h. The reaction mixture was

poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl (4-butoxy-2-isobutyl-1-oxo-6-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.42 g, 89.4%) as crystals.

Melting point 155-159°C.

10 Elemental analysis for  $C_{29}H_{38}N_2O_4$

Calculated: C, 72.77; H, 8.00; N, 5.85.

Found: C, 72.52; H, 7.81; N, 5.73.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.98 (6H, d,  $J=6.6$  Hz), 1.03 (3H, t,  $J=7.3$  Hz), 1.47 (9H, s), 1.48-1.69 (2H, m), 1.81-1.95 (2H, m), 2.13-2.26 (1H, m), 3.92 (2H, t,  $J=6.6$  Hz), 4.02 (2H, d,  $J=7.4$  Hz), 4.55 (2H, d,  $J=5.4$  Hz), 4.78 (1H, bs), 7.39-7.56 (3H, m), 7.66-7.75 (3H, m), 7.89 (1H, d,  $J=1.4$  Hz), 8.49 (1H, d,  $J=8.6$  Hz).

(2) Tert-butyl (4-butoxy-2-isobutyl-1-oxo-6-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.34 g, 0.7 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 1 h. The reaction was concentrated under reduced pressure, and the residue was crystallized from methanol - diisopropyl ether to give 3-(aminomethyl)-4-butoxy-2-isobutyl-6-phenyl-1(2H)-isoquinolinone hydrochloride (0.28 g, 96.6%) as crystals.

Melting point 180-181°C.

Elemental analysis for  $C_{24}H_{31}N_2O_2Cl$

30 Calculated: C, 69.46; H, 7.53; N, 6.75.

Found: C, 69.15; H, 7.70; N, 6.81.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.90 (6H, d,  $J=6.6$  Hz), 1.00 (3H, t,  $J=7.4$  Hz), 1.51-1.69 (2H, m), 1.80-2.12 (3H, m), 3.90-4.05 (4H, m), 4.22 (2H, s), 7.45-7.62 (3H, m), 7.77-7.82 (2H, m), 7.91-7.95 (2H, m), 8.37 (1H, d,  $J=8.8$  Hz), 8.71 (3H, bs).

**Example 264**

3-(Aminomethyl)-4-butoxy-2-isobutyl-6-[(E)-2-(1,3-thiazol-4-yl)ethenyl]-1(2H)-isoquinolinone hydrochloride  
(1) A mixture of triphenyl(1,3-thiazol-4-

- 5 ylmethyl)phosphonium chloride (0.44 g, 1.1 mmol), potassium carbonate (0.15 g, 1.1 mmol) and tert-butyl (4-butoxy-6-formyl-2-isobutyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.47 g, 1.1 mmol) in N,N-dimethylformamide (10 ml) was stirred at room  
10 temperature for 10 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting crystals were recrystallized from ethyl  
15 acetate - diisopropyl ether to give tert-butyl {4-butoxy-2-isobutyl-1-oxo-6-[(E)-2-(1,3-thiazol-4-yl)ethenyl]-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.46 g, 80.7%) as crystals.

Melting point 141-142°C.

- 20 Elemental analysis for  $C_{29}H_{37}N_3O_4S \cdot 0.5H_2O$

Calculated: C, 65.39; H, 7.19; N, 7.89.

Found: C, 65.58; H, 7.33; N, 8.11.

- $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.97 (6H, d,  $J=7.0$  Hz), 1.06 (3H, t,  $J=7.3$  Hz), 1.47 (9H, s), 1.48-1.69 (2H, m), 1.83-1.97  
25 (2H, m), 2.11-2.25 (1H, m), 3.89 (2H, t,  $J=6.6$  Hz), 3.99 (2H, d,  $J=7.4$  Hz), 4.52 (2H, d,  $J=5.4$  Hz), 4.77 (1H, bs), 7.31 (1H, d,  $J=16.0$  Hz), 7.32 (1H, d,  $J=16.0$  Hz), 7.32 (1H, d,  $J=1.8$  Hz), 7.62-7.74 (3H, m), 8.39 (1H, d,  $J=8.8$  Hz), 8.87 (1H, d,  $J=1.4$  Hz).

- 30 (2) Tert-butyl {4-butoxy-2-isobutyl-1-oxo-6-[(E)-2-(1,3-thiazol-4-yl)ethenyl]-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.16 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate solution (5 ml). The solution was stirred at  
35 room temperature for 1 h. The reaction was concentrated under reduced pressure, and the residue was

recrystallized from methanol - diisopropyl ether to give 3-(aminomethyl)-4-butoxy-2-isobutyl-6-[(E)-2-(1,3-thiazol-4-yl)ethenyl]-1(2H)-isoquinolinone hydrochloride (0.11 g, 84.6%) as crystals.

5 Melting point 164-166°C.

Elemental analysis for  $C_{24}H_{30}N_3O_2ClS \cdot 0.75H_2O$

Calculated: C, 56.52; H, 6.42; N, 8.24.

Found: C, 56.44; H, 6.41; N, 8.21.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.89 (6H, d, J=6.6 Hz), 1.06 (3H, t, J=7.1 Hz), 1.50-1.68 (2H, m), 1.83-2.10 (3H, m), 3.91-4.00 (4H, m), 4.18 (2H, d, J=4.4 Hz), 7.56 (1H, d, J=16.2 Hz), 7.67 (1H, d, J=16.2 Hz), 7.84 (1H, s), 7.87 (1H, d, J=1.8 Hz), 7.94 (1H, dd, J=1.8, 8.6 Hz), 8.26 (1H, d, J=8.6 Hz), 8.69 (3H, bs), 9.22 (1H, s).

15 **Example 265**

3-(Aminomethyl)-4-butoxy-2-isobutyl-6-[2-(1,3-thiazol-4-yl)ethyl]-1(2H)-isoquinolinone hydrochloride

(1) A suspension of tert-butyl {4-butoxy-2-isobutyl-1-oxo-6-[(E)-2-(1,3-thiazol-4-yl)ethenyl]-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.21 g, 0.4 mmol) and 5% palladium carbon (0.2 g) in tetrahydrofuran (10 ml) was stirred under a hydrogen atmosphere at room temperature for 2 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl {4-butoxy-2-isobutyl-1-oxo-6-[2-(1,3-thiazol-4-yl)ethyl]-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.20 g, 95.2%) as crystals.

30 Melting point 103-104°C.

Elemental analysis for  $C_{29}H_{39}N_2C_4S \cdot 0.5H_2O$

Calculated: C, 65.14; H, 7.54; N, 7.86.

Found: C, 65.34; H, 7.53; N, 8.12.

$^1H$ -NMR(CDCl<sub>3</sub>)  $\delta$ : 0.95 (6H, d, J=7.0 Hz), 1.04 (3H, t, J=7.3 Hz), 1.46 (9H, s), 1.46-1.65 (2H, m), 1.77-1.91 (2H, m), 2.09-2.24 (1H, m), 3.22 (4H, s), 3.79 (2H, t,

J=6.6 Hz), 3.89 (2H, d, J=7.2 Hz), 4.50 (2H, d, J=5.6 Hz), 4.70 (1H, bs), 6.86 (1H, d, J=2.0 Hz), 7.33 (1H, dd, J=1.6, 8.2 Hz), 7.44 (1H, d, J=1.6 Hz), 8.33 (1H, d, J=8.2 Hz), 8.78 (1H, d, J=2.0 Hz).

- 5 (2) Tert-butyl {4-butoxy-2-isobutyl-1-oxo-6-[2-(1,3-thiazol-4-yl)ethyl]-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.16 g, 0.3 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room  
10 temperature for 1 h. The reaction was concentrated under reduced pressure to give 3-(aminomethyl)-4-butoxy-2-isobutyl-6-[2-(1,3-thiazol-4-yl)ethyl]-1(2H)-isoquinolinone hydrochloride (0.13 g, 92.9%) as an amorphous solid.

- 15 Elemental analysis for  $C_{24}H_{32}N_3O_2ClS \cdot 2.5H_2O$

Calculated: C, 56.85; H, 7.35; N, 8.29.

Found: C, 56.80; H, 7.20; N, 8.13.

- $^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.87 (6H, d, J=6.6 Hz), 1.00 (3H, t, J=7.3 Hz), 1.48-1.67 (2H, m), 1.77-1.87 (2H, m), 1.96-  
20 2.05 (1H, m), 3.16-3.21 (4H, m), 3.84 (2H, t, J=6.3 Hz), 3.94 (2H, d, J=6.0 Hz), 4.15 (2H, d, J=5.1 Hz), 7.35-7.38 (1H, m), 7.49-7.51 (2H, m), 8.18 (1H, d, J=8.7 Hz), 8.56 (3H, bs), 9.11-9.18 (1H, m).

#### Example 266

- 25 6-Amino-3-(aminomethyl)-4-butoxy-2-neopentyl-1(2H)-isoquinolinone dihydrochloride

- (1) 9H-Fluoren-9-ylmethyl 4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl}-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinylcarbamate (1.14 g, 87.7%) as an  
30 amorphous solid.

[synthesized according to the method similar to that in Example 82(1) from 4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl}-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinecarboxylic acid (0.92 g, 2 mmol)]

- 35  $^1H$ -NMR(CDCl<sub>3</sub>)  $\delta$ : 0.99 (9H, s), 1.01 (3H, t, J=7.4 Hz), 1.44 (9H, s), 1.45-1.62 (2H, m), 1.79-1.90 (2H, m), 3.86

(2H, t, J=6.4 Hz), 4.10 (2H, bs), 4.29 (1H, t, J=6.4 Hz), 4.54-4.62 (4H, m), 4.72 (1H, bs), 7.10 (1H, bs), 7.26-7.46 (5H, m), 7.63 (2H, d, J=7.3 Hz), 7.79 (2H, d, J=7.3 Hz), 8.78 (1H, s), 8.32 (1H, d, J=8.8 Hz).

- 5 (2) Tert-butyl (6-amino-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.66 g, 90.4%) as an amorphous solid.[synthesized according to the method similar to that in Example 82(2) from 9H-fluoren-9-ylmethyl 4-butoxy-3-[(tert-butoxycarbonyl)amino]methyl}-2-neopentyl-1-oxo-1,2-
- 10 dihydro-6-isoquinolinylcarbamate (1.11 g, 1.7 mmol)]  
<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.98 (9H, s), 1.02 (3H, t, J=7.4 Hz), 1.44 (9H, s), 1.50-1.60 (2H, m), 1.70-1.88 (2H, m), 3.83 (2H, t, J=6.5 Hz), 4.19 (2H, bs), 4.53 (2H, d, J=5.4 Hz),  
15 4.67 (1H, bs), 6.78-6.81 (2H, m), 8.20 (1H, d, J=9.0 Hz).

- (3) 6-amino-3-(aminomethyl)-4-butoxy-2-neopentyl-1(2H)-isoquinolinone dihydrochloride (0.19 g, 95.0%) as an amorphous solid.[synthesized according to the method similar to that in Example 82(3) from tert-butyl (6-
- 20 amino-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.21 g, 0.5 mmol)]

Elemental analysis for C<sub>19</sub>H<sub>31</sub>N<sub>3</sub>O<sub>2</sub>Cl<sub>2</sub>

Calculated: C, 56.43; H, 7.73; N, 10.39.

Found: C, 56.71; H, 8.05; N, 10.00.

- 25 <sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.88 (9H, s), 1.02 (3H, t, J=6.2 Hz), 1.48-1.59 (2H, m), 1.77-1.91 (2H, m), 3.88 (2H, t, J=5.9 Hz), 4.00 (2H, bs), 4.19 (2H, bs), 6.53 (3H, bs), 6.98-7.04 (2H, m), 8.03 (1H, d, J=8.4 Hz), 8.54 (3H, bs).

#### Example 267

- 30 N-[3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl]acetamide hydrochloride  
(1) Tert-butyl [6-(acetylamino)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.30 g, 63.8%) as crystals.[synthesized according to the method  
35 similar to that in Example 88(1) from tert-butyl (6-amino-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-

isoquinolinyl)methylcarbamate (0.43 g, 1 mmol)]

Melting point 120-121°C.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.99 (9H, s), 1.01 (3H, t, J=7.0 Hz),  
1.45 (9H, s), 1.47-1.66 (2H, m), 1.79-1.93 (2H, m), 2.26  
5 (3H, s), 3.88 (2H, t, J=6.6 Hz), 4.14 (2H, bs), 4.56 (2H,  
d, J=5.6 Hz), 4.86 (1H, bs), 7.34 (1H, d, J=8.6 Hz),  
7.88 (1H, bs), 8.15 (1H, s), 8.28 (1H, d, J=8.6 Hz).

(2) N-[3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-  
dihydro-6-isoquinolinyl]acetamide (0.19 g, 95.0%) as  
10 crystals.

[synthesized according to the method similar to that in  
Example 88(2) from tert-butyl [6-(acetylamino)-4-butoxy-  
2-neopentyl-1-oxo-1,2-dihydro-3-  
isoquinolinyl]methylcarbamate (0.24 g, 0.5 mmol)]

15 Melting point 191-193°C.

Elemental analysis for C<sub>21</sub>H<sub>32</sub>N<sub>3</sub>O<sub>3</sub>Cl 0.5H<sub>2</sub>O

Calculated: C, 60.20; H, 7.94; N, 10.03.

Found: C, 60.43; H, 8.07; N, 9.90.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.90 (9H, s), 0.99 (3H, t, J=6.2 Hz),  
20 1.43-1.67 (2H, m), 1.72-1.93 (2H, m), 2.13 (3H, s), 3.92  
(2H, s), 4.05 (2H, bs), 4.22 (2H, s), 7.70 (1H, d, J=8.6  
Hz), 8.08 (1H, d, J=8.6 Hz), 8.27 (1H, s), 8.52 (3H, bs),  
10.63 (1H, s).

#### Example 268

25 3-(Aminomethyl)-7-(benzyloxy)-2-isobutyl-4-phenyl-1(2H)-  
isoquinolinone hydrochloride

(1) Ethyl 7-(benzyloxy)-2-isobutyl-1-oxo-4-  
trifluoromethanesulfonyloxy-1,2-dihydro-3-  
isoquinolinecarboxylate (24.01 g, 91.0%) as crystals.

30 [synthesized according to the method similar to that in  
Example 154(2) from ethyl 7-(benzyloxy)-4-hydroxy-2-  
isobutyl-1-oxo-1,2-dihydro-3-isoquinolinecarboxylate  
(19.77 g, 50 mmol)]

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.90 (6H, d, J=6.6 Hz), 1.44 (3H, t,  
35 J=7.1 Hz), 1.96-2.07 (1H, m), 4.12 (2H, d, J=7.2 Hz),  
4.45 (2H, q, J=7.1 Hz), 5.21 (2H, s), 7.30-7.48 (6H, m),



7.74 (1H, d, J=9.0 Hz), 7.96 (1H, d, J=9.0 Hz).

(2) Ethyl 7-(benzyloxy)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinecarboxylate (16.21 g, 79.1%) as crystals.

- 5 [synthesized according to the method similar to that in Example 154(3) from ethyl 7-(benzyloxy)-2-isobutyl-1-oxo-4-trifluoromethanesulfonyloxy-1,2-dihydro-3-isoquinolinecarboxylate (23.74 g, 45 mmol) and phenylboronic acid (6.58 g, 54 mmol)]

- 10 Melting point 107-108°C.

Elemental analysis for  $C_{29}H_{29}NO_4$

Calculated: C, 76.46; H, 6.42; N, 3.07.

Found: C, 76.45; H, 6.54; N, 3.06.

- $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.87 (3H, d, J=7.2 Hz), 0.94 (6H, d, J=6.6 Hz), 2.05-2.23 (1H, m), 3.93 (2H, q, J=7.2 Hz), 4.05 (2H, d, J=7.4 Hz), 5.21 (2H, s), 7.13-7.50 (12H, m), 8.03 (1H, d, J=2.2 Hz).

- (3) 7-(Benzyloxy)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinecarboxylic acid (11.21 g, 74.9%) as an amorphous solid.

[synthesized according to the method similar to that in Example 154(4) from ethyl 7-(benzyloxy)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinecarboxylate (15.94 g, 35 mmol)]

- 25  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.90 (6H, d, J=6.8 Hz), 2.14-2.28 (1H, m), 4.01 (2H, d, J=7.8 Hz), 5.15 (2H, s), 7.11-7.48 (12H, m), 7.66 (1H, d, J=1.8 Hz).

(4) 7-(Benzyloxy)-3-(hydroxymethyl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone (9.31 g, 90.1%) as crystals.

- 30 [synthesized according to the method similar to that in Example 154(5) from 7-(benzyloxy)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinecarboxylic acid (10.69 g, 25 mmol)]

Melting point 125-126°C.

- 35 Elemental analysis for  $C_{27}H_{27}NO_3 \cdot 0.5H_2O$

Calculated: C, 76.75; H, 6.68; N, 3.32.

Found: C, 76.36; H, 6.46; N, 3.24.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.99 (6H, d, J=7.0 Hz), 2.05 (1H, bs),  
2.20-2.34 (1H, m), 4.25 (2H, d, J=7.2 Hz), 4.46 (2H, d,  
J=3.6 Hz), 5.11 (2H, s), 6.92 (1H, d, J=8.8 Hz), 7.11  
5 (1H, dd, J=2.6, 8.8 Hz), 7.29-7.56 (10H, m), 7.91 (1H, d,  
J=2.6 Hz).

(5) 7-(Benzyloxy)-3-(chloromethyl)-2-isobutyl-4-phenyl-  
1(2H)-isoquinolinone (7.44 g, 86.2%) as an oil.

[synthesized according to the method similar to that in  
10 Example 154(6) from 7-(benzyloxy)-3-(hydroxymethyl)-2-  
isobutyl-4-phenyl-1(2H)-isoquinolinone (8.27 g, 20  
mmol)]

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.02 (6H, d, J=7.0 Hz), 2.16-2.31 (1H,  
m), 4.20 (2H, d, J=7.4 Hz), 4.42 (2H, s), 5.20 (2H, s),  
15 6.96 (1H, d, J=8.8 Hz), 7.13-7.54 (11H, m), 8.01 (1H, d,  
J=2.8 Hz).

(6) 2-[[7-(Benzyloxy)-2-isobutyl-1-oxo-4-phenyl-1,2-  
dihydro-3-isoquinolinyl]methyl]-1H-isoindole-1,3(2H)-  
dione (8.74 g, 94.8%) as an amorphous solid.

20 [synthesized according to the method similar to that in  
Example 154(7) from 7-(benzyloxy)-3-(chloromethyl)-2-  
isobutyl-4-phenyl-1(2H)-isoquinolinone (7.34 g, 17  
mmol)]

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.01 (6H, d, J=6.6 Hz), 2.17-2.31 (1H,  
25 m), 4.08 (2H, d, J=7.0 Hz), 4.78 (2H, s), 5.19 (2H, s),  
6.92 (1H, d, J=9.0 Hz), 7.17 (1H, dd, J=2.8, 9.0 Hz),  
7.21-7.49 (10H, m), 7.66-7.78 (4H, m), 7.98 (1H, d,  
J=2.8 Hz).

(7) Tert-butyl [7-(benzyloxy)-2-isobutyl-1-oxo-4-phenyl-  
30 1,2-dihydro-3-isoquinolinyl]methylcarbamate (7.56 g,  
92.2%) as crystals.

[synthesized according to the method similar to that in  
Example 154(8) from 2-[[7-(benzyloxy)-2-isobutyl-1-oxo-  
4-phenyl-1,2-dihydro-3-isoquinolinyl]methyl]-1H-  
35 isoindole-1,3(2H)-dione (8.68 g, 16 mmol)]

Melting point 181-182°C.

Elemental analysis for  $C_{32}H_{36}N_2O_4$

Calculated: C, 74.97; H, 7.08; N, 5.46.

Found: C, 74.94; H, 7.14; N, 5.31.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.01 (6H, d,  $J=6.8$  Hz), 1.43 (9H, s),  
5 2.20-2.31 (1H, m), 4.08 (2H, d,  $J=7.4$  Hz), 4.19 ((2H, d,  
 $J=5.2$  Hz), 4.55 (1H, bs), 5.16 (2H, s), 6.89 (1H, d,  
 $J=8.8$  Hz), 7.15 (1H, dd,  $J=2.8, 8.8$  Hz), 7.24-7.55 (10H,  
m), 7.96 (1H, d,  $J=2.8$  Hz).

(8) 3-(Aminomethyl)-7-(benzyloxy)-2-isobutyl-4-phenyl-  
10 1(2H)-isoquinolinone hydrochloride (0.21 g, 95.5%) as  
crystals.

[synthesized according to the method similar to that in  
Example 214(3) from tert-butyl [7-(benzyloxy)-2-  
isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-  
15 isoquinolinyl]methylcarbamate (0.26 g, 0.5 mmol)]

Melting point 242-243°C.

Elemental analysis for  $C_{27}H_{29}N_2O_2Cl$

Calculated: C, 72.23; H, 6.51; N, 6.24.

Found: C, 71.99; H, 6.54; N, 6.05.

20  $^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.92 (6H, d,  $J=6.6$  Hz), 1.99-2.19 (1H,  
m), 3.85 (2H, d,  $J=4.8$  Hz), 4.09 (2H, s), 5.26 (2H, s),  
6.85 (1H, d,  $J=8.8$  Hz), 7.33-7.57 (11H, m), 7.85 (1H, d,  
 $J=2.6$  Hz), 8.58 (3H, bs).

#### Example 269

25 3-(Aminomethyl)-7-hydroxy-2-isobutyl-4-phenyl-1(2H)-  
isoquinolinone hydrochloride

(1) Tert-butyl (7-hydroxy-2-isobutyl-1-oxo-4-phenyl-1,2-  
dihydro-3-isoquinolinyl)methylcarbamate (5.75 g, 97.3%)  
as crystals.

30 [synthesized according to the method similar to that in  
Example 154(9) from tert-butyl [7-(benzyloxy)-2-  
isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-  
isoquinolinyl]methylcarbamate (7.14 g, 14 mmol)]

Melting point 232-233°C.

35 Elemental analysis for  $C_{25}H_{30}N_2O_4$

Calculated: C, 71.07; H, 7.16; N, 6.63.

Found: C, 70.81; H, 7.22; N, 6.35.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 1.02 (6H, d,  $J=7.0$  Hz), 1.42 (9H, s),  
2.21-2.35 (1H, m), 4.11 (2H, d,  $J=7.2$  Hz), 4.22 (2H, d,  
 $J=5.2$  Hz), 4.52 (1H, bs), 6.91 (1H, d,  $J=8.8$  Hz), 7.16  
5 (1H, dd,  $J=2.6, 8.8$  Hz), 7.23-7.28 (2H, m), 7.44-7.55  
(3H, m), 8.52 (1H, d,  $J=2.8$  Hz), 8.90 (1H, s).

(2) 3-(Aminomethyl)-7-hydroxy-2-isobutyl-4-phenyl-1(2H)-  
isoquinolinone hydrochloride (0.17 g, 94.4%) as crystals.

[synthesized according to the method similar to that in  
10 Example 214(3) from tert-butyl (7-hydroxy-2-isobutyl-1-  
oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate  
(0.21 g, 0.5 mmol)]

Melting point 259-261°C.

Elemental analysis for  $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_2\text{Cl} \cdot 0.25\text{H}_2\text{O}$

15 Calculated: C, 66.11; H, 6.52; N, 7.71.

Found: C, 66.00; H, 6.51; N, 7.53.

$^1\text{H-NMR}(\text{DMSO}-d_6)$   $\delta$ : 0.91 (6H, d,  $J=6.6$  Hz), 2.00-2.16 (1H,  
m), 3.85 (2H, s), 4.05 (2H, d,  $J=7.0$  Hz), 6.76 (1H, d,  
 $J=8.8$  Hz), 7.13 (1H, dd,  $J=2.8, 8.8$  Hz), 7.35-7.39 (2H,  
20 m), 7.47-7.60 (2H, m), 7.68 (1H, d,  $J=2.8$  Hz), 8.48 (3H,  
bs), 10.27 (1H, bs).

#### Example 270

3-(Aminomethyl)-7-ethoxy-2-isobutyl-4-phenyl-1(2H)-  
isoquinolinone hydrochloride

25 (1) Tert-butyl (7-ethoxy-2-isobutyl-1-oxo-4-phenyl-1,2-  
dihydro-3-isoquinolinyl)methylcarbamate (0.39 g, 86.7%)  
as crystals.

[synthesized according to the method similar to that in  
Example 154(10) from tert-butyl (7-hydroxy-2-isobutyl-1-  
30 oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate  
(0.42 g, 1 mmol) and 2-iodoethane (0.12 ml, 1.5 mmol)]

Melting point 163-164°C.

Elemental analysis for  $\text{C}_{27}\text{H}_{34}\text{N}_2\text{O}_4$

Calculated: C, 71.97; H, 7.61; N, 6.22.

35 Found: C, 71.67; H, 7.41; N, 6.28.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 1.01 (6H, d,  $J=6.6$  Hz), 1.42 (9H, s),

1.44 (3H, t, J=7.4 Hz), 2.19-2.35 (1H, m), 4.06-4.21 (6H, m), 4.48 (1H, bs), 6.88 (1H, d, J=9.0 Hz), 7.09 (1H, dd, J=2.7, 9.0 Hz), 7.23-7.27 (2H, m), 7.46-7.53 (3H, m), 7.86 (1H, d, J=2.6 Hz).

- 5 (2) 3-(Aminomethyl)-7-ethoxy-2-isobutyl-4-phenyl-1(2H)-isoquinolinone hydrochloride (0.18 g, 66.7%) as crystals.

[synthesized according to the method similar to that in Example 214(3) from tert-butyl (7-ethoxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate

- 10 (0.32 g, 0.7 mmol)]

Melting point 154-155°C.

Elemental analysis for  $C_{22}H_{27}N_2O_2Cl \cdot 0.25H_2O$

Calculated: C, 67.51; H, 7.08; N, 7.16.

Found: C, 67.30; H, 7.04; N, 7.10.

- 15  $^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.92 (6H, d, J=6.6 Hz), 1.37 (3H, t, J=6.8 Hz), 2.01-2.19 (1H, m), 3.86 (2H, s), 4.07-4.20 (4H, m), 6.83 (1H, d, J=9.0 Hz), 7.27 (1H, dd, J=2.8, 9.0 Hz), 7.37-7.41 (2H, m), 7.54-7.57 (3H, m), 7.73 (1H, d, J=2.8 Hz), 8.53 (3H, s).

- 20 **Example 271**

3-(Aminomethyl)-2-isobutyl-7-(2-methoxyethoxy)-4-phenyl-1(2H)-isoquinolinone hydrochloride

- (1) Tert-butyl [2-isobutyl-7-(2-methoxyethoxy)-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.34 g, 70.8%) as crystals.

[synthesized according to the method similar to that in Example 154(10) from tert-butyl (7-hydroxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.42 g, 1 mmol) and bromoethyl methyl ether (0.14 ml,

- 30 1.5 mmol)]

Melting point 124-125°C.

Elemental analysis for  $C_{28}H_{36}N_2O_5$

Calculated: C, 69.98; H, 7.55; N, 5.83.

Found: C, 69.81; H, 7.37; N, 5.96.

- 35  $^1H$ -NMR(CDCl $_3$ )  $\delta$ : 1.00 (6H, d, J=6.6 Hz), 1.42 (9H, s), 2.19-2.35 (1H, m), 3.45 (3H, s), 3.74-3.80 (2H, m), 4.08

(2H, d, J=7.0 Hz), 4.19-4.27 (4H, m), 4.51 (1H, bs), 6.89 (1H, d, J=8.6 Hz), 7.16 (1H, dd, J=2.8, 8.6 Hz), 7.19-7.27 (2H, m), 7.47-7.52 (3H, m), 7.86 (1H, d, J=2.8 Hz).

- 5 (2) 3-(Aminomethyl)-2-isobutyl-7-(2-methoxyethoxy)-4-phenyl-1(2H)-isoquinolinone hydrochloride (0.21 g, 84.0%) as crystals.

[synthesized according to the method similar to that in Example 214(3) from tert-butyl [2-isobutyl-7-(2-methoxyethoxy)-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.28 g, 0.6 mmol)]  
Melting point 148-149°C.

Elemental analysis for  $C_{23}H_{29}N_2O_3Cl \cdot 0.5H_2O$

Calculated: C, 64.85; H, 7.10; N, 6.58.

- 15 Found: C, 65.25; H, 7.21; N, 6.73.

$^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.92 (6H, d, J=6.2 Hz), 1.99-2.21 (1H, m), 3.31 (3H, s), 3.63-3.69 (2H, m), 3.86 (2H, s), 4.07-4.10 (2H, m), 4.22 (2H, s), 6.84 (1H, d, J=9.2 Hz), 7.28-7.40 (3H, m), 7.54-7.62 (3H, m), 7.74 (1H, s), 8.56  
20 (3H, s).

#### Example 272

2-[[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-7-isoquinolinyl]oxy]acetamide hydrochloride

- (1) Tert-butyl [7-(2-amino-2-oxoethoxy)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate  
25 (0.19 g, 40.4%) as crystals.

[synthesized according to the method similar to that in Example 154(10) from tert-butyl (7-hydroxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate  
30 (0.42 g, 1 mmol) and 2-iodoacetamide (0.27 g, 1.5 mmol)]  
Melting point 211-212°C.

Elemental analysis for  $C_{27}H_{33}N_3O_5$

Calculated: C, 67.62; H, 6.94; N, 8.76.

Found: C, 67.38; H, 6.69; N, 8.87.

- 35  $^1H$ -NMR(CDCl $_3$ )  $\delta$ : 1.00 (6H, d, J=6.6 Hz), 1.43 (9H, s), 2.18-2.34 (1H, m), 4.08 (2H, d, J=7.4 Hz), 4.20 (2H, d,

J=5.4 Hz), 4.51 (1H, bs), 4.58 (2H, s), 5.86 (1H, bs), 6.57 (1H, bs), 6.94 (1H, d, J=8.8 Hz), 7.13 (1H, d, J=8.8 Hz), 7.23-7.27 (2H, m), 7.49-7.52 (3H, m), 7.90 (1H, s).

- 5 (2) 2-{{3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-7-isoquinolinyl}oxy}acetamide hydrochloride (0.11 g, 91.2%) as crystals. [synthesized according to the method similar to that in Example 214(3) from tert-butyl [7-(2-amino-2-oxoethoxy)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.14 g, 0.3 mmol)] Melting point 244-245°C.

Elemental analysis for  $C_{22}H_{26}N_3O_3Cl \cdot 1.75H_2O$

Calculated: C, 59.06; H, 6.65; N, 9.39.

Found: C, 59.21; H, 6.52; N, 9.33.

- 15  $^1H$ -NMR(DMSO- $d_6$ )  $\delta$ : 0.92 (6H, d, J=6.6 Hz), 1.99-2.19 (1H, m), 3.85 (2H, d, J=4.2 Hz), 4.09 (2H, d, J=7.0 Hz), 4.58 (2H, s), 6.85 (1H, d, J=8.8 Hz), 7.33 (1H, dd, J=2.6, 8.8 Hz), 7.36-7.41 (2H, m), 7.56-7.60 (3H, m), 7.69 (1H, bs), 7.72 (1H, d, J=2.6 Hz), 8.64 (3H, s).

20 **Example 273**

3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-7-isoquinolinecarboxamide hydrochloride

(1) Tert-butyl (2-isobutyl-1-oxo-4-phenyl-7-trifluoromethanesulfonyloxy-1,2-dihydro-3-

- 25 isoquinolinyl)methylcarbamate (5.01 g, 90.4%) as an amorphous solid. [synthesized according to the method similar to that in Example 155(1) from tert-butyl (7-hydroxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (4.22 g, 10 mmol)]

- 30  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.01 (6H, d, J=6.6 Hz), 1.43 (9H, s), 2.20-2.29 (1H, m), 4.09 (2H, d, J=7.5 Hz), 4.23 (2H, d, J=5.4 Hz), 4.46 (1H, bs), 7.06 (1H, d, J=9.0 Hz), 7.22-7.27 (2H, m), 7.36 (1H, dd, J=2.7, 9.0 Hz), 7.42-7.56 (3H, m), 8.34 (1H, d, J=2.7 Hz).

- 35 (2) Methyl 3-{[(tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-7-

isoquinolinecarboxylate (3.11 g, 74.4%) as crystals.

[synthesized according to the method similar to that in Example 155(2) from tert-butyl (2-isobutyl-1-oxo-4-phenyl-7-trifluoromethanesulfonyloxy-1,2-dihydro-3-

5 isoquinolinyl)methylcarbamate (4.99 g, 9 mmol)]

Melting point 134-135°C.

Elemental analysis for  $C_{27}H_{32}N_2O_5$

Calculated: C, 69.81; H, 6.94; N, 6.03.

Found: C, 69.46; H, 7.04; N, 5.81.

10  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 1.01 (6H, d, J=6.6 Hz), 1.43 (9H, s), 2.05-2.28 (1H, m), 3.93 (3H, s), 4.10 (2H, d, J=7.5 Hz), 4.22 (2H, d, J=5.4 Hz), 4.61 (1H, bs), 6.98 (1H, d, J=8.7 Hz), 7.24-7.28 (2H, m), 7.46-7.57 (3H, m), 8.02 (1H, dd, J=1.8, 8.7 Hz), 9.10 (1H, d, J=1.8 Hz).

15 (3) 3-[[ (Tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-7-isoquinolinecarboxylic acid (2.49 g, 92.2%) as crystals.

[synthesized according to the method similar to that in Example 155(3) from methyl 3-[[ (tert-

20 butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-7-isoquinolinecarboxylate (2.79 g, 6 mmol)]

Melting point 246°C.

Elemental analysis for  $C_{26}H_{30}N_2O_5 \cdot 0.25H_2O$

Calculated: C, 68.62; H, 6.76; N, 6.16.

25 Found: C, 68.88; H, 6.83; N, 5.87.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.91 (6H, d, J=6.6 Hz), 1.38 (9H, s), 2.12-2.26 (1H, m), 3.91 (2H, d, J=6.6 Hz), 3.99 (2H, d, J=4.2 Hz), 6.99 (1H, d, J=8.8 Hz), 7.34 (1H, bs), 7.39-7.42 (2H, m), 7.46-7.56 (3H, m), 8.09 (1H, dd, J=2.0, 8.8 Hz), 8.87 (1H, d, J=2.0 Hz).

30 (4) Tert-butyl [7-(aminocarbonyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.86 g, 95.6%) as crystals. [synthesized according to the method similar to that in Example 155(4) from 3-[[ (tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-7-isoquinolinecarboxylic acid (0.90 g, 2



mmol)]

Melting point 232-233°C.

Elemental analysis for  $C_{26}H_{31}N_3O_4 \cdot 0.5H_2O$

Calculated: C, 68.10; H, 7.03; N, 9.16.

5 Found: C, 68.31; H, 7.07; N, 8.75.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (6H, d,  $J=6.6$  Hz), 1.43 (9H, s),  
2.10-2.24 (1H, m), 4.08 (2H, d,  $J=7.0$  Hz), 4.22 (2H, d,  
 $J=5.2$  Hz), 4.76 (1H, bs), 5.96 (1H, bs), 6.74 (1H, bs),  
7.02 (1H, d,  $J=8.6$  Hz), 7.25-7.30 (2H, m), 7.45-7.56 (3H,  
10 m), 8.05 (1H, dd,  $J=1.4, 8.6$  Hz), 8.78 (1H, d,  $J=1.4$  Hz).

(5) 3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-  
dihydro-7-isoquinolinecarboxamide hydrochloride (0.18 g,  
94.7%) as crystals. [synthesized according to the method  
similar to that in Example 155(5) from tert-butyl [7-  
15 (aminocarbonyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-  
isoquinolinyl]methylcarbamate (0.23 g, 0.5 mmol)]

Melting point 254-256°C.

Elemental analysis for  $C_{21}H_{24}N_3O_2Cl \cdot H_2O$

Calculated: C, 63.87; H, 6.38; N, 10.64.

20 Found: C, 63.76; H, 6.29; N, 10.30.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.94 (6H, d,  $J=6.6$  Hz), 2.04-2.19 (1H,  
m), 3.89 (2H, d,  $J=4.4$  Hz), 4.13 (2H, d,  $J=7.0$  Hz), 6.94  
(1H, d,  $J=8.6$  Hz), 7.37-7.44 (2H, m), 7.54-7.64 (4H, m),  
8.16 (1H, dd,  $J=1.8, 8.6$  Hz), 8.30 (1H, bs), 8.67 (3H,  
25 bs), 8.85 (1H, d,  $J=1.8$  Hz).

#### Example 274

3-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-  
dihydro-6-isoquinolinyl]propanamide hydrochloride

(1) A suspension of ethyl (E)-3-(3-([(tert-  
30 butoxycarbonyl)amino]methyl)-2-isobutyl-1-oxo-4-phenyl-  
1,2-dihydro-6-isoquinolinyl)-2-propenoate (0.90g, 1.8  
mmol) and 5% palladium carbon (0.5 g) in ethanol (10 ml)  
and tetrahydrofuran (10 ml) was stirred under a hydrogen  
atmosphere at room temperature for 2 h. The catalyst was  
35 filtered off, and the filtrate was concentrated under  
reduced pressure. The residue was purified by silica gel

column chromatography to give ethyl 3-(3-([(tert-butoxycarbonyl)amino]methyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)propanoate (0.82 g, 90.1%) as an amorphous solid.

5 <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.99 (6H, d, J=6.6 Hz), 1.19 (3H, t, J=7.1 Hz), 1.42 (9H, s), 2.18-2.29 (1H, m), 2.51 (2H, t, J=7.8 Hz), 2.90 (2H, t, J=7.8 Hz), 4.01-4.12 (4H, m), 4.19 (2H, d, J=5.6 Hz), 4.40 (1H, bs), 6.74 (1H, d, J=1.6 Hz), 7.21-7.26 (2H, m), 7.31 (1H, dd, J=1.6, 8.4  
10 Hz), 7.46-7.53 (3H, m), 8.39 (1H, d, J=8.4 Hz).

(2) To a solution of ethyl 3-(3-([(tert-butoxycarbonyl)amino]methyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)propanoate (0.61g, 1.2 mmol) in tetrahydrofuran (5 ml) and ethanol (5 ml) was added  
15 1N sodium hydroxide solution (3 ml). The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous  
20 magnesium sulfate and concentrated under reduced pressure. The resulting crystals were recrystallized from ethyl acetate - diisopropyl ether to give 3-(3-([(tert-butoxycarbonyl)amino]methyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)propanoic acid (0.52  
25 g, 91.2%) as crystals.

Melting point 182-183°C.

Elemental analysis for C<sub>28</sub>H<sub>34</sub>N<sub>2</sub>O<sub>5</sub>

Calculated: C, 70.12; H, 7.36; N, 5.84.

Found: C, 70.21; H, 7.55; N, 5.68.

30 <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.98 (6H, d, J=6.9 Hz), 1.42 (9H, s), 2.15-2.27 (1H, m), 2.58 (2H, t, J=7.8 Hz), 2.91 (2H, t, J=7.8 Hz), 4.06 (2H, d, J=6.0 Hz), 4.19 (2H, d, J=5.2 Hz), 4.53 (1H, bs), 6.76 (1H, s), 7.22-7.25 (2H, m), 7.31 (1H, d, J=8.8 Hz), 7.46-7.52 (3H, m), 8.37 (1H, d,  
35 J=8.8 Hz).

(3) A solution of 3-(3-([(tert-

butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)propanoic acid (0.33 g, 0.7 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.27 g, 1.4 mmol) and 1-

- 5 hydroxybenzotriazole ammonium salt (0.21 g, 1.4 mmol) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 2 h. The resulting reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous  
10 magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [6-(3-amino-3-oxopropyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.31 g, 93.9%) as  
15 crystals.

Melting point 239-240°C.

Elemental analysis for  $C_{28}H_{35}N_3O_4 \cdot 0.25H_2O$

Calculated: C, 69.76; H, 7.42; N, 8.72.

Found: C, 69.54; H, 7.41; N, 8.58.

- 20  $^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (6H, d,  $J=6.6$  Hz), 1.42 (9H, s), 2.13-2.29 (1H, m), 2.43 (2H, t,  $J=8.0$  Hz), 2.92 (2H, t,  $J=8.0$  Hz), 4.05 (2H, d,  $J=7.4$  Hz), 4.19 (2H, d,  $J=5.2$  Hz), 4.54 (1H, bs), 5.42 (2H, bs), 6.75 (1H, d,  $J=1.4$  Hz), 7.21-7.30 (3H, m), 7.21-7.30 (3H, m), 7.46-7.57 (3H, m),  
25 8.33-8.37 (1H, m).

- (4) 3-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]propanamide hydrochloride (0.20 g, 95.3%) as crystals. [synthesized according to the method similar to that in Example 214(3) from tert-butyl  
30 [6-(3-amino-3-oxopropyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.24 g, 0.5 mmol)]

Melting point 186-187°C.

- $^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.91 (6H, d,  $J=6.6$  Hz), 2.02-2.16 (1H, m),  
35 2.26 (2H, t,  $J=7.2$  Hz), 2.76 (2H, t,  $J=7.2$  Hz), 3.86 (2H, s), 4.08 (2H, s), 6.72 (1H, s), 6.75 (1H, bs), 7.29

(1H, bs), 7.38-7.40 (2H, m), 7.45 (1H, d, J=8.4 Hz),  
7.55-7.59 (3H, m), 8.25 (1H, d, J=8.4 Hz), 8.57 (3H, bs).

**Example 275**

2-(2-([3-(Aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-  
5 dihydro-6-isoquinolinyl]oxy)ethyl)-1H-isoindole-1,3(2H)-  
dione hydrochloride

To a solution of tert-butyl (4-butoxy-6-hydroxy-2-  
isobutyl-1-oxo-4-1,2-dihydro-3-  
isoquinolinyl)methylcarbamate (2.09 g, 5 mmol), N-(2-  
10 hydroxyethyl)phthalimide (1.15 g, 6 mmol) and tri-n-  
butylphosphine (2.5 ml, 10 mmol) in tetrahydrofuran (30  
ml) was added 1,1'-(azodicarbonyl)dipiperidine (2.52 g,  
10 mmol), and the mixture was stirred at room  
temperature for 6 h. The reaction mixture was  
15 concentrated under reduced pressure, and the residue was  
purified by silica gel column chromatography. The  
resulting crystals were dissolved in a solution of 4N  
hydrogen chloride in ethyl acetate (5 ml). The solution  
was stirred at room temperature for 2 h. The reaction  
20 mixture was concentrated under reduced pressure, and the  
residue was crystallized from methanol - diisopropyl  
ether to give 2-(2-([3-(aminomethyl)-4-butoxy-2-  
isobutyl-1-oxo-1,2-dihydro-6-isoquinolinyl]oxy)ethyl)-  
1H-isoindole-1,3(2H)-dione hydrochloride (0.14 g, 93.3%)  
25 as crystals.

Melting point 176-177°C.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.86 (6H, d, J=6.6 Hz), 0.99 (3H, t,  
J=7.3 Hz), 1.46-1.64 (2H, m), 1.77-2.06 (3H, m), 3.88-  
3.94 (4H, m), 4.04 (2H, t, J=5.5 Hz), 4.15 (2H, s), 4.41  
30 (2H, t, J=5.5 Hz), 7.05 (1H, d, J=2.4 Hz), 7.14 (1H, dd,  
J=2.4, 9.0 Hz), 7.82-7.92 (4H, m), 8.15 (1H, d, J=9.0  
Hz), 8.53 (3H, bs).

**Example 276**

3-[3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-  
35 dihydro-6-isoquinolinyl]propanamide hydrochloride  
(1) Ethyl 3-(3-([(tert-butoxycarbonyl)amino]methyl)-4-

butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl)propanoate (0.68 g, 88.3%) as an oil.

[synthesized according to the method similar to that in Example 274(1) from ethyl (E)-3-(3-((tert-

5 butoxycarbonyl)amino)methyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl)-2-propenoate (0.77 g, 1.5 mmol)]

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.99 (9H, s), 1.04 (3H, t, J=7.2 Hz), 1.24 (3H, t, J=7.0 Hz), 1.45 (9H, s), 1.49-1.68 (2H, m),  
10 1.80-1.94 (2H, m), 2.70 (2H, t, J=7.8 Hz), 3.11 (2H, t, J=7.8 Hz), 3.86 (2H, t, J=6.6 Hz), 4.10 (2H, bs), 4.14 (2H, q, J=7.0 Hz), 4.58 (2H, s), 4.62 (1H, bs), 7.35 (1H, dd, J=1.6, 8.2 Hz), 7.51 (1H, d, J=1.6 Hz), 8.33 (1H, d, J=8.4 Hz).

15 (2) 3-(3-((Tert-butoxycarbonyl)amino)methyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl)propanoic acid (0.40 g, 90.9%) as crystals.

[synthesized according to the method similar to that in Example 274(2) from ethyl 3-(3-((tert-

20 butoxycarbonyl)amino)methyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl)propanoate (0.46g, 0.9 mmol)]

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.98 (9H, s), 1.03 (3H, t, J=7.4 Hz), 1.45 (9H, s), 1.46-1.67 (2H, m), 1.79-1.92 (2H, m), 2.77  
25 (2H, t, J=7.4 Hz), 3.11 (2H, t, J=7.4 Hz), 3.84 (2H, t, J=6.4 Hz), 4.14 (2H, bs), 4.57 (2H, d, J=5.8 Hz), 4.75 (1H, bs), 7.34 (1H, dd, J=1.6, 8.5 Hz), 7.52 (1H, d, J=1.6 Hz), 8.32 (1H, d, J=8.5 Hz).

(3) Tert-butyl [6-(3-amino-3-oxopropyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.19 g, 86.4%) as crystals.

[synthesized according to the method similar to that in Example 274(3) from 3-(3-((tert-

35 butoxycarbonyl)amino)methyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl)propanoic acid (0.22 g, 0.45

mmol)]

Melting point 87-88°C.

Elemental analysis for  $C_{27}H_{41}N_3O_5$

Calculated: C, 66.50; H, 8.47; N, 8.62.

5 Found: C, 66.25; H, 8.35; N, 8.54.

$^1H$ -NMR( $CDCl_3$ )  $\delta$ : 0.99 (9H, s), 1.04 (3H, t,  $J=7.4$  Hz),  
1.45 (9H, s), 1.52-1.72 (2H, m), 1.80-1.94 (2H, m), 2.60  
(2H, t,  $J=7.7$  Hz), 3.13 (2H, t,  $J=7.7$  Hz), 3.86 (2H, t,  
 $J=6.6$  Hz), 4.14 (2H, bs), 4.56 (2H, d,  $J=5.4$  Hz), 4.73  
10 (1H, bs), 5.50 (2H, bs), 7.32 (1H, d,  $J=8.2$  Hz), 7.52  
(1H, s), 8.29 (1H, d,  $J=8.2$  Hz).

(4) 3-[3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-  
dihydro-6-isoquinolinyl]propanamide hydrochloride (0.11  
g, 91.7%) as crystals. [synthesized according to the  
15 method similar to that in Example 274(4) from tert-butyl  
[6-(3-amino-3-oxopropyl)-4-butoxy-2-neopentyl-1-oxo-1,2-  
dihydro-3-isoquinolinyl]methylcarbamate (0.14 g, 0.3  
mmol)]

Melting point 151-153°C.

20 Elemental analysis for  $C_{27}H_{41}N_3O_5Cl$

Calculated: C, 66.50; H, 8.47; N, 8.62.

Found: C, 66.25; H, 8.35; N, 8.54.

$^1H$ -NMR( $DMSO-d_6$ )  $\delta$ : 0.90 (9H, s), 1.00 (3H, t,  $J=7.3$  Hz),  
1.51-1.62 (2H, m), 1.78-1.91 (2H, m), 2.46 (2H, t,  $J=7.4$   
25 Hz), 3.00 (2H, t,  $J=7.4$  Hz), 3.93 (2H, t,  $J=6.1$  Hz),  
4.08 (2H, bs), 4.23 (2H, d,  $J=4.0$  Hz), 6.82 (1H, bs),  
7.44 (1H, bs), 7.47 (1H, d,  $J=8.2$  Hz), 7.58 (1H, s),  
8.17 (1H, d,  $J=8.2$  Hz), 8.53 (3H, bs).

#### Example 277

30 [3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-  
6-isoquinolinyl]acetonitrile hydrochloride

(1) To a solution of p-toluenesulfonylmethyl isocyanide  
(0.94 g, 4.8 mmol) in 1,2-dimethoxyethane (20 ml) were  
added potassium t-butoxide (0.90 g, 8 mmol) and tert-  
35 butyl (4-butoxy-6-formyl-2-neopentyl-1-oxo-1,2-dihydro-  
3-isoquinolinyl)methylcarbamate (1.78 g, 4 mmol) at -

70°C, and the mixture was stirred at -70°C for 1 h. To the mixture was added methanol (30 ml), and the mixture was refluxed for 30 min. The reaction mixture was poured into water and extracted with ethyl acetate. The extract  
5 was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give tert-butyl [4-butoxy-6-(cyanomethyl)-2-neopentyl-1-oxo-1,2-dihydro-3-  
10 isoquinolinyl]methylcarbamate (0.66 g, 36.3%) as an amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.00 (9H, s), 1.04 (3H, t, J=7.4 Hz), 1.45 (9H, s), 1.51-1.66 (2H, m), 1.82-1.92 (2H, m), 3.88 (2H, t, J=6.2 Hz), 3.92 (2H, s), 4.18 (2H, bs), 4.58 (2H,  
15 d, J=5.0 Hz), 4.72 (1H, bs), 7.40 (1H, dd, J=1.8, 8.4 Hz), 7.70 (1H, d, J=1.8 Hz), 8.40 (1H, d, J=8.4 Hz).

(2) [3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl]acetonitrile hydrochloride (0.10 g, 90.9%) as crystals [synthesized according to the  
20 method similar to that in Example 214(3) from tert-butyl [4-butoxy-6-(cyanomethyl)-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.14 g, 0.3 mmol)].

Melting point 169-171°C.

Elemental analysis for C<sub>21</sub>H<sub>30</sub>N<sub>3</sub>O<sub>2</sub>Cl 0.25H<sub>2</sub>O

25 Calculated: C, 63.62; H, 7.73; N, 10.60.

Found: C, 63.70; H, 7.85; N, 10.59.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.90 (9H, s), 1.00 (3H, t, J=7.4 Hz), 1.52-1.63 (2H, m), 1.80-1.91 (2H, m), 3.94 (2H, t, J=6.6 Hz), 4.14 (2H, bs), 4.26 (2H, bs), 4.33 (2H, s), 7.57  
30 (1H, dd, J=1.4, 8.0 Hz), 7.78 (1H, d, J=1.4 Hz), 8.29 (1H, d, J=8.0 Hz), 8.54 (3H, bs).

#### Example 278

2-[3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl]acetamide hydrochloride

35 (1) To a solution of tert-butyl [4-butoxy-6-(cyanomethyl)-2-neopentyl-1-oxo-1,2-dihydro-3-

isoquinolinyl)methylcarbamate (0.45g, 1 mmol) in ethanol (20 ml) was added a solution of potassium hydroxide (0.40 g, 10 mmol) in water (5 ml). The mixture was refluxed for 10h. The reaction mixture was poured into water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give crude amorphous solid. A solution of the amorphous solid, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.19 g, 1 mmol) and 1-hydroxybenzotriazole ammonium salt (0.15 g, 1 mmol) in N,N-dimethylformamide (10 ml) was stirred for 2h at room temperature. The resulting reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give tert-butyl [6-(2-amino-2-oxoethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.13 g, 54.2%) as crystals.

Melting point 197-198°C.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.99 (9H, s), 1.04 (3H, t, J=7.4 Hz), 1.45 (9H, s), 1.46-1.64 (2H, m), 1.80-1.90 (2H, m), 3.74 (2H, s), 3.87 (2H, t, J=6.5 Hz), 4.14 (2H, bs), 4.57 (2H, d, J=5.4 Hz), 4.71 (1H, bs), 5.47 (1H, bs), 5.54 (1H, bs), 7.40 (1H, dd, J=1.4, 8.0 Hz), 7.60 (1H, d, J=1.4 Hz), 8.38 (1H, d, J=8.0 Hz).

(2) Tert-butyl [6-(2-amino-2-oxoethyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-3-isoquinolinyl)methylcarbamate (95 mg, 0.2 mmol) was dissolved in a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The solution was stirred at room temperature for 2h. The reaction was concentrated under reduced pressure, and the residue was crystallized from methanol - diisopropyl ether to give 2-[3-(aminomethyl)-



4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl]acetamide hydrochloride (75 mg, 91.5%) as crystals.

Melting point 163-165°C.

- 5 <sup>1</sup>H-NMR(DMSO-d<sub>6</sub>) δ: 0.90 (9H, s), 1.00 (3H, t, J=7.5 Hz), 1.52-1.59 (2H, m), 1.80-1.90 (2H, m), 3.61 (2H, s), 3.93 (2H, s), 4.02 (2H, bs), 4.24 (2H, s), 7.03 (1H, bs), 7.50 (1H, d, J=8.5 Hz), 7.67 (1H, s), 7.69 (1H, bs), 8.20 (1H, d, J=8.5 Hz).

10 **Example 279**

[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]acetonitrile hydrochloride

- (1) To a mixture of tert-butyl [6-(hydroxymethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.33 g, 0.75 mmol),  
15 triethylamine (0.18 mL, 1.1 mmol), N,N,N',N'-tetramethylethylenediamine (0.011 mL, 0.075 mmol), toluene (6 mL) and tetrahydrofuran (6 mL) was added dropwise a solution of methanesulfonyl chloride (0.088  
20 mL, 1.1 mmol) in toluene (4 mL) under ice-cooling. The mixture was stirred under ice-cooling for 30 min, the reaction mixture was poured into 0.1N hydrochloric acid (50 mL) and extracted with ethyl acetate (50 mL). The extract was washed with brine, dried over anhydrous  
25 magnesium sulfate and concentrated under reduced pressure to give (3-[(tert-butoxycarbonyl)amino]methyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-6-yl)methyl methanesulfonate (0.39 g, 100 %) as colorless powder.

- 30 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.01 (6H, d, J= 7.0 Hz), 1.43 (9H, s), 2.15-2.30 (1H, m), 2.91 (3H, s), 4.09 (2H, d, J= 7.0 Hz), 4.22 (2H, d, J= 6.0 Hz), 4.45 (1H, br), 5.18 (2H, s), 6.93 (1H, d, J= 1.0 Hz), 7.15-7.30 (2H, m), 7.45-7.60 (4H, m), 8.51 (1H, d, J= 8.6 Hz).

- 35 (2) To a mixture of (3-[(tert-butoxycarbonyl)amino]methyl)-2-isobutyl-1-oxo-4-phenyl-

1,2-dihydroisoquinolin-6-yl)methyl methanesulfonate (0.39 g, 0.75 mmol) in acetonitrile (5 mL) and tetrahydrofuran (4 mL) were added trimethylsilyl cyanide (0.15 mL, 1.1 mmol) and a solution of 1.0 M  
5 tetrabutylammonium fluoride in tetrahydrofuran (1.1 mL), and then the mixture was stirred at 80°C for 30 min. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate= 5:2 (v/v)) to  
10 give tert-butyl [6-(cyanomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.25 g, 75%) as a colorless oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.01 (6H, d, J= 6.8 Hz), 1.43 (9H, s), 2.15-2.30 (1H, m), 3.71 (2H, s), 4.09 (2H, d, J= 6.8 Hz),  
15 4.21 (2H, d, J= 5.4 Hz), 4.46 (1H, br), 6.86 (1H, d, J= 1.8 Hz), 7.20-7.30 (2H, m), 7.43 (1H, dd, J= 1.8, 8.4 Hz), 7.50-7.60 (3H, m), 8.49 (1H, d, J= 8.4 Hz).

(3) To a solution of tert-butyl [6-(cyanomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-  
20 isoquinolinyl]methylcarbamate (0.13 g, 0.29 mmol) in ethyl acetate (4 mL) was added a 4N hydrogen chloride ethyl acetate solution (1 mL), and the mixture was stirred at room temperature for 12 h. The reaction was concentrated under reduced pressure, and the residue was  
25 crystallized from diisopropyl ether and washed with diisopropyl ether (5 mL X 2) to give [3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]acetonitrile hydrochloride (0.096 g, 88%) as a pale yellow powder.

30 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 0.92 (6H, d, J= 6.6 Hz), 1.95-2.20 (1H, m), 3.87 (2H, bs), 4.06 (2H, d, J= 5.4 Hz), 4.13 (2H, s), 6.85-6.95 (1H, m), 7.35-7.45 (3H, m), 7.50-7.65 (3H, m), 8.36 (1H, d, J= 8.0 Hz), 8.43 (3H, bs).

Melting point: 142-144°C

35 **Example 280**

N-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-

5 dihydro-6-isoquinolinyl]-N'-methoxyurea hydrochloride  
(1) To a solution of 3-[[tert-butoxycarbonyl)amino]methyl]-2-isobutyl-1-oxo-4-phenyl-  
1,2-dihydroisoquinoline-6-carboxylic acid (0.15 g, 0.33  
5 mmol) in N,N-dimethylformamide (5 mL) was added  
diphenylphosphoryl azide (0.09 mL, 0.40 mmol) and  
triethylamine (0.056 mL, 0.40 mmol), and the mixture was  
stirred at room temperature for 2 h. The reaction  
mixture was poured into water (50 mL) and extracted with  
10 ethyl acetate (30 mL X 2). The organic layers were  
combined, washed with water (50 mL) and brine (20 mL),  
dried over anhydrous magnesium sulfate and concentrated  
under reduced pressure. The residue was dissolved in  
toluene (20 mL), and the solution was refluxed for 1 h.  
15 The reaction mixture was allowed to cool to room  
temperature, and a mixture of O-methylhydroxyamine  
hydrochloride (0.088 g, 0.40 mmol) and triethylamine  
(0.056 mL, 0.40 mmol) in N,N-dimethylformamide (2 mL)  
was added thereto. The resulting reaction mixture was  
20 stirred at room temperature for 1 h and then poured into  
water (100 mL). The organic layer was separated and the  
aqueous layer was extracted twice with ethyl acetate.  
The organic layers were combined, washed with 0.1M  
aqueous citric acid solution (20 mL) and brine (10 mL),  
25 dried over anhydrous magnesium sulfate and concentrated  
under reduced pressure. The residue was purified by  
silica gel column chromatography (n-hexane:ethyl  
acetate= 1:1 (v/v)) to give tert-butyl (2-isobutyl-6-  
30 dihydro-3-isoquinolinyl)methylcarbamate (0.13 g, 81%)  
as a colorless oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.00 (6H, d, J= 6.9 Hz), 1.43 (9H, s),  
2.20-2.35 (1H, m), 3.74 (3H, d, J= 0.6 Hz), 4.05 (2H, d,  
J= 6.9 Hz), 4.19 (2H, d, J= 5.5 Hz), 4.59 (1H, br), 6.95  
35 (1H, bs), 7.22 (1H, br), 7.25-7.30 (3H, m), 7.45-7.70  
(4H, m), 8.40 (1H, d, J= 8.7 Hz).

(2) N-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-N'-methoxyurea hydrochloride (0.049 g, 46%) as a pale yellow powder[synthesized according to the method similar to that in Example 279

5 (3) from tert-butyl (2-isobutyl-6-  
{[(methoxyamino)carbonyl]amino}-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.12 g, 0.25 mmol)]

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 0.91 (6H, d, J= 6.6 Hz), 2.00-2.20  
10 (1H, m), 3.55 (3H, s), 3.83 (2H, bs), 4.02 (2H, d, J= 6.6 Hz), 7.25 (1H, d, J=1.8 Hz), 7.30-7.40 (2H, m), 7.50-7.60 (3H, m), 7.82 (1H, dd, J= 1.8, 8.8 Hz), 8.21 (1H, d, J= 8.8 Hz), 8.39 (3H, bs), 9.29 (1H, s), 9.60 (1H, s).

15 Melting point: 297-299°C

#### Example 281

3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarbohydrazide dihydrochloride

(1) A mixture of methyl 3-[(tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-phenyl-  
20 1,2-dihydroisoquinoline-6-carboxylate (0.12 g, 0.27 mmol) and hydrazine monohydrate (0.65 mL, 13 mmol) in methanol (6 mL) was stirred in a sealed tube at 75°C for 2 h. The reaction mixture was concentrated, and the  
25 residue was recrystallized from water - methanol to give tert-butyl [6-(hydrazinocarbonyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.12 g, 96%) as colorless crystals.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.00 (6H, d, J= 7.0 Hz), 1.43 (9H, s),  
30 2.20-2.30 (1H, m), 2.48 (3H, br), 4.08 (2H, d, J= 7.0 Hz), 4.20 (2H, d, J= 5.2 Hz), 4.70 (1H, br), 7.20-7.30 (3H, m), 7.45-7.55 (3H, m), 7.69 (1H, d, J= 5.4 Hz), 8.43 (1H, d, J= 8.6 Hz).

(2) 3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarbohydrazide dihydrochloride  
35 (0.095 g, 95%) as a pale yellow powder.

[synthesized according to the method similar to that in Example 279 (3) from tert-butyl [6-(hydrazinocarbonyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.11 g, 0.29 mmol)]

5 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 0.93 (6H, d, J= 6.6 Hz), 2.00-2.20 (1H, m), 3.88 (2H, bs), 4.09 (2H, d, J= 7.0 Hz), 7.35-7.45 (3H, m), 7.55-7.65 (3H, m), 8.00 (1H, dm, J= 8.4 Hz), 8.45 (1H, d, J=8.4 Hz), 8.56 (3H, bs), 11.62 (1H, bs).

10 Melting point: 291-292°C

#### Example 282

3-(Aminomethyl)-2-isobutyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)-4-phenyl-1(2H)-isoquinolinone

(1) A mixture of tert-butyl [6-(hydrazinocarbonyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.23 g, 0.50 mmol) and trimethyl orthoacetate (2.0 mL, 11 mmol) in 1-butanol (10 mL) was refluxed for 20 min. To the reaction mixture was added 1,8-diazabicyclo[5.4.0]-7-undecene (0.075 mL, 0.50 mmol), and then the mixture was refluxed for 1h. The resulting reaction mixture was neutralized with acetic acid (0.040 mL, 0.70 mmol) and concentrated under reduced pressure. The residue was partitioned between water (10 mL) and ethyl acetate (30 mL). The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate= 2:1 (v/v)) to give tert-butyl [2-isobutyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.22 g, 91%) as crystals.

25 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.02 (6H, d, J= 7.2 Hz), 1.43 (9H, s), 2.15-2.35 (1H, m), 2.57 (3H, s), 4.10 (2H, d, J= 7.2 Hz), 4.22 (2H, d, J= 5.4 Hz), 4.57 (1H, br), 7.20-7.35 (2H, m), 7.50-7.65 (4H, m), 8.05 (1H, dm, J= 8.4 Hz), 8.58 (1H, dd, J= 1.4, 8.4 Hz).

30

(2) A mixture of tert-butyl [2-isobutyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.20 g, 0.41 mmol) and 4N hydrogen chloride ethyl acetate solution (4 mL) was stirred for 17h at room temperature. The reaction mixture was concentrated, the residue was washed with diisopropyl ether (5 mL X 2) to give a pale yellow powder. The powder was added to aqueous saturated sodium hydrogencarbonate (30 mL), the resulting mixture was extracted with ethyl acetate-tetrahydrofuran (1:1, v/v, 50 mL X 2). The organic layers were combined, washed with brine (25 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:methanol= 20:1 (v/v)) and recrystallized from n-hexane-ethyl acetate to give 3-(aminomethyl)-2-isobutyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)-4-phenyl-1(2H)-isoquinolinone (0.11 g, 72%) as pale yellow crystals.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.02 (6H, d, J= 6.6 Hz), 2.15-2.40 (1H, m), 2.57 (3H, s), 3.69 (2H, bs), 4.24 (2H, d, J= 7.4 Hz), 7.25-7.35 (2H, m), 7.45-7.60 (3H, m), 7.62 (1H, d, J=1.6 Hz), 8.05 (1H, dd, J= 1.6, 8.4 Hz), 8.59 (1H, d, J=8.4 Hz).

Melting point: 179-181°C

#### Example 283

2-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]acetamide hydrochloride

(1) A mixture of tert-butyl [6-(cyanomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.13 g, 0.29 mmol), 2N potassium hydroxide solution (5 mL) and ethanol (5 mL) was refluxed for 4 h. The reaction mixture was diluted with 0.1N sodium hydroxide solution (100 mL) and washed with ethyl acetate (20 mL X 2). The aqueous layer was separated, acidified with 1N hydrochloric acid and

extracted with ethyl acetate (100 mL X 2). The organic layers were combined, washed with brine (20 mL), saturated aqueous sodium hydrogencarbonate (50 mL) and brine (50 mL), dried over anhydrous magnesium sulfate  
5 and concentrated under reduced pressure to give (3-  
{[(tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-6-yl)acetic acid (0.36 g, 87%) as a pale yellow oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.98 (6H, d, J= 6.6 Hz), 1.42 (9H, s),  
10 2.15-2.35 (1H, m), 3.60 (2H, s), 3.95-4.25 (4H, m), 4.48 (1H, br), 6.81 (1H, d, J= 1.2 Hz), 7.10-7.30 (3H, m), 7.38 (1H, d, J= 7.5 Hz), 7.45-7.55 (2H, m), 8.40 (1H, dm, J= 7.5 Hz).

(2) A mixture of (3-  
15 {[(tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-6-yl)acetic acid (0.15 g, 0.32 mmol), 1-hydroxybenzotriazole ammonium salt (0.074 g, 0.48 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.093 g,  
20 0.48 mmol) in N,N-dimethylformamide (10 mL) was stirred at room temperature for 17 h. The reaction mixture was poured into 0.1N aqueous citric acid solution (50 mL) and extracted with ethyl acetate (25 mL X 2). The organic layers were combined, washed with 0.1N aqueous  
25 citric acid solution (50 mL), saturated aqueous sodium hydrogencarbonate (50 mL) and brine (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate) to give tert-butyl  
30 [6-(2-amino-2-oxoethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.12 g, 81%) as colorless crystals.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.00 (6H, d, J= 6.6 Hz), 1.42 (9H, s),  
2.15-2.30 (1H, m), 3.54 (2H, s), 4.00-4.25 (4H, m), 4.44  
35 (1H, br), 5.31 (2H, br), 6.82 (1H, m), 7.20-7.30 (2H, m), 7.35-7.55 (4H, m), 8.46 (1H, dm, J= 8.0 Hz).

(3) 2-[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]acetamide hydrochloride (0.090 g, 90%) as pale yellow crystals.

[synthesized according to the method similar to that in  
5 Example 279 (3) from tert-butyl [6-(2-amino-2-oxoethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.11 g, 0.25 mmol)]  
<sup>1</sup>H-NMR (CD<sub>3</sub>OD) δ: 1.00 (6H, d, J= 6.6 Hz), 2.10-2.30 (1H, m), 3.52 (2H, s), 4.05-4.20 (4H, m), 7.00 (1H, d, J= 1.2  
10 Hz), 7.35-7.45 (2H, m), 7.50-7.65 (5H, m), 8.37 (1H, d, J= 8.0 Hz).

Melting point: 231-233°C

#### Example 284

2-([3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-  
15 dihydro-6-isoquinolinyl]methyl)-1H-isoindole-1,3(2H)-dione hydrochloride

(1) To a solution of (3-((tert-butoxycarbonyl)amino)methyl)-4-butoxy-2-neopentyl-1-oxo-1,2-dihydro-6-isoquinolinyl)methyl methanesulfonate (1.1  
20 g, 2.11 mmol) in N,N-dimethylformamide (20 mL) was added potassium phthalimide (0.47 g, 2.5 mmol), and the mixture was stirred at room temperature for 17 h. The reaction mixture was poured into water (200 mL) and extracted with ethyl acetate (100 mL X 2). The organic  
25 layers were combined, washed with 0.2N hydrochloric acid (100 mL), saturated aqueous sodium hydrogencarbonate (50 mL) and brine (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column  
30 chromatography (n-hexane:ethyl acetate= 5:2 (v/v)) to give tert-butyl {6-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.99 g, 84%) as colorless crystals.

35 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.98 (6H, d, J= 6.6 Hz), 1.42 (9H, s), 2.10-2.30 (1H, m), 4.05 (2H, d, J= 7.4 Hz), 4.20 (2H, d,



J= 7.4 Hz), 4.42 (1H, br), 4.80 (2H, s), 6.90 (1H, d, J= 1.2 Hz), 7.15-7.25 (2H, m), 7.35-7.45 (4H, m), 7.65-7.75 (2H, m), 7.75-7.85 (2H, m), 8.40 (1H, d, J= 8.0 Hz).

(2) 2-([3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]methyl)-1H-isoindole-1,3(2H)-dione hydrochloride (0.10 g, 100%) as a colorless powder.

[synthesized according to the method similar to that in Example 279 (3) from tert-butyl {6-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.11 g, 0.20 mmol)]

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 0.90 (6H, d, J= 6.6 Hz), 1.95-2.20 (1H, m), 3.87 (2H, bs), 4.04 (2H, d, J= 5.4 Hz), 4.77 (2H, s), 6.65-6.75 (1H, m), 7.25-7.30 (2H, m), 7.35-7.45 (3H, m), 7.52 (1H, dm, J= 8.2 Hz), 7.87 (4H, s), 8.29 (1H, d, J=8.2 Hz), 8.31 (3H, bs).

Melting point: 196-199°C

#### Example 285

N-([3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]methyl)acetamide hydrochloride  
(1) A mixture of tert-butyl {6-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl}methylcarbamate (0.85 g, 1.5 mmol) and hydrazine monohydrate (0.6 mL, 12 mmol) in ethanol (20 mL) and tetrahydrofuran (10 mL) was stirred at room temperature for 17 h. The reaction mixture was filtered, and the filtrate was concentrated. After the residue was dissolved in ethyl acetate (50 mL), the solution was filtrated to remove insoluble material.  
The filtrate was concentrated to give tert-butyl [6-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.82 g) as a crude pale yellow oil. To a solution of the crude oil (0.16 g) in tetrahydrofuran (2 mL) was added acetic anhydride (0.034 mL, 0.36 mmol), and then the mixture was stirred at room temperature for 4 h. The reaction mixture was washed

with water (4 mL) and concentrated. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate= 4:1 (v/v)) to give tert-butyl {6-[(acetylamino)methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.090 g, 63%) as a pale yellow solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.00 (6H, d, J= 6.6 Hz), 1.43 (9H, s), 1.96 (3H, s), 2.25-2.35 (1H, m), 4.06 (2H, d, J= 7.6 Hz), 4.19 (2H, d, J= 5.4 Hz), 4.38 (2H, d, J= 6.6 Hz), 4.59 (1H, br), 5.84 (1H, br), 6.76 (1H, m), 7.20-7.55 (6H, m), 8.38 (1H, dm, J= 8.4 Hz).

(2) N-{[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]methyl}acetamide hydrochloride (0.068 g, 96%) as a pale yellow powder.

[synthesized according to the method similar to that in Example 279 (3) from tert-butyl {6-[(acetylamino)methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.082 g, 0.17 mmol)]

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 0.91 (6H, d, J= 6.6 Hz), 1.75 (3H, s), 1.95-2.20 (1H, m), 3.87 (2H, bs), 4.04 (2H, d, J= 6.6 Hz), 4.20 (2H, d, J= 6.6 Hz), 6.73 (1H, s), 7.30-7.40 (2H, m), 7.44 (1H, dd, J= 1.6, 8.4 Hz), 7.50-7.60 (3H, m), 8.28 (1H, d, J=8.4 Hz), 8.30-8.45 (4H, m).

Melting point: 134-139°C

#### Example 286

N-{[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]methyl}-2-methylpropanamide hydrochloride

(1) To a solution of crude tert-butyl [6-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl]methylcarbamate (0.16 g) (Example 285) in tetrahydrofuran (2 mL) was added isobutyryl chloride (0.038 mL, 0.36 mmol) and triethylamine (0.050 mL, 0.36 mmol), and the mixture was stirred at room temperature for 4 h. The reaction mixture was washed with water (4

mL) and concentrated. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate= 4:1 (v/v)) to give tert-butyl {2-isobutyl-6-  
[(isobutyrylamino)methyl]-1-oxo-4-phenyl-1,2-dihydro-3-  
5 isoquinolinyl)methylcarbamate (0.11 g, 75%) as a pale yellow solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.99 (6H, d, J= 6.6 Hz), 1.07 (6H, d, J= 7.0 Hz), 1.43 (9H, s), 2.15-2.35 (2H, m), 4.06 (2H, d, J= 7.2 Hz), 4.20 (2H, d, J= 5.4 Hz), 4.41 (2H, d, J= 6.2  
10 Hz), 4.58 (1H, br), 5.79 (1H, br), 6.77 (1H, d, J= 1.2 Hz), 7.20-7.60 (6H, m), 8.38 (1H, dm, J= 8.2 Hz).

(2) N-{{[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]methyl}-2-methylpropanamide hydrochloride (0.091 g, 98%) as a pale yellow powder.

15 [synthesized according to the method similar to that in Example 279 (3) from tert-butyl {2-isobutyl-6-  
[(isobutyrylamino)methyl]-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.11 g, 0.21 mmol)]

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 0.86 (6H, d, J= 6.6 Hz), 0.91 (6H, d, J= 6.6 Hz), 1.95-2.35 (2H, m), 3.84 (2H, bs), 4.06 (2H, d, J= 7.0 Hz), 4.24 (2H, d, J= 5.8 Hz), 6.75 (1H, s),  
20 7.30-7.40 (2H, m), 7.43 (1H, dd, J= 1.0, 8.4 Hz), 7.45-7.60 (3H, m), 8.27 (1H, bs), 8.27 (1H, d, J= 8.4 Hz), 8.52 (3H, bs).

25 Melting point: 189-191°C

#### Example 287

Ethyl [3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)methylcarbamate hydrochloride

(1) To a solution of crude tert-butyl [6-(aminomethyl)-  
30 2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.16 g) (Example 285) in tetrahydrofuran (2 mL) were added ethyl chloroformate (0.035 mL, 0.36 mmol) and triethylamine (0.050 mL, 0.36 mmol), and the mixture was stirred at room temperature  
35 for 4 h. The reaction mixture was washed with water (4 mL) and concentrated. The residue was purified by silica

gel column chromatography (n-hexane:ethyl acetate= 4:1 (v/v)) to give ethyl (3-[(tert-butoxycarbonyl)amino]methyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)methylcarbamate (0.13 g,

5 87%) as pale yellow powder.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.00 (6H, d, J= 6.6 Hz), 1.21 (3H, t, J= 7.0 Hz), 1.42 (9H, s), 2.15-2.35 (1H, m), 4.07 (2H, d, J= 7.8 Hz), 4.09 (2H, q, J= 7.0 Hz), 4.19 (2H, d, J= 7.4 Hz), 4.31 (2H, d, J= 6.6 Hz), 4.49 (1H, br), 4.96 (1H, br), 6.79 (1H, s), 7.20-7.55 (6H, m), 8.42 (1H, d, J= 8.4 Hz).

(2) Ethyl [3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)methylcarbamate hydrochloride (0.092 g, 88%) as a colorless powder.

15 [synthesized according to the method similar to that in Example 279 (3) from ethyl (3-[(tert-butoxycarbonyl)amino]methyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)methylcarbamate (0.12 g, 0.24 mmol)]

20 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 0.91 (6H, d, J= 6.6 Hz), 1.11 (3H, t, J= 7.4 Hz), 2.00-2.20 (1H, m), 3.86 (2H, bs), 3.91 (2H, q, J= 7.4 Hz), 4.07 (2H, d, J= 7.8 Hz), 4.13 (2H, d, J= 6.0 Hz), 6.77 (1H, s), 7.30-7.40 (2H, m), 7.45 (1H, dd, J= 1.6, 8.2 Hz), 7.50-7.60 (3H, m), 7.64 (1H, d, J= 6.0 Hz), 8.28 (1H, d, J= 8.2 Hz), 8.55 (3H, bs).

Melting point: 184-187°C

#### Example 288

N-[[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)methyl]methanesulfonamide

30 hydrochloride

(1) To a solution of crude tert-butyl [6-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.16 g) (Example 285) in tetrahydrofuran (2 mL) was added methanesulfonyl

35 chloride (0.028 mL, 0.36 mmol) and triethylamine (0.050 mL, 0.36 mmol), and the mixture was stirred at room

temperature for 4 h. The reaction mixture was washed with water (4 mL) and concentrated. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate= 2:1 (v/v)) to give tert-butyl (2-isobutyl-6-  
5 isobutyl-6-[[[(methylsulfonyl)amino]methyl]-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate (0.13 g, 84%) as a pale yellow oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.00 (6H, d, J= 6.6 Hz), 1.43 (9H, s), 2.15-2.35 (1H, m), 2.80 (3H, s), 4.07 (2H, d, J= 7.2 Hz),  
10 4.20 (2H, d, J= 5.8 Hz), 4.29 (2H, d, J= 6.6 Hz), 4.52 (1H, br), 4.71 (1H, bt, J= 5.8 Hz), 6.86 (1H, d, J= 1.2 Hz), 7.20-7.30 (2H, m), 7.44 (1H, dd, J= 1.6 8.0 Hz), 7.45-7.60 (3H, m), 8.44 (1H, d, J= 8.0 Hz).

(2) N-[[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-  
15 dihydro-6-isoquinolinyl)methyl]methanesulfonamide hydrochloride (0.097 g, 100%) as a pale yellow powder.

[synthesized according to the method similar to that in Example 279 (3) from tert-butyl (2-isobutyl-6-  
[[[(methylsulfonyl)amino]methyl]-1-oxo-4-phenyl-1,2-  
20 dihydro-3-isoquinolinyl)methylcarbamate (0.11 g, 0.21 mmol)]

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 0.91 (6H, d, J= 6.6 Hz), 1.95-2.20 (1H, m), 2.80 (3H, s), 3.86 (2H, bs), 4.07 (2H, d, J= 7.0 Hz), 4.14 (2H, d, J= 6.2 Hz), 6.88 (1H, s), 7.35-  
25 7.45 (2H, m), 7.50-7.65 (4H, m), 7.63 (1H, t, J= 6.2 Hz), 8.32 (1H, d, J=8.0 Hz), 8.55 (3H, bs).

Melting point: 117-120°C

#### Example 289

3,6-Bis(aminomethyl)-2-isobutyl-4-phenyl-1(2H)-  
30 isoquinolinone dihydrochloride

(1) To a solution of crude tert-butyl [6-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-  
isoquinolinyl)methylcarbamate (0.16 g)(Example 286) in tetrahydrofuran (2 mL) was added di-t-butyl dicarbonate  
35 (0.086 mL, 0.36 mmol), and the mixture was stirred at room temperature for 4 h. The reaction mixture was

washed with water (4 mL) and concentrated. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate= 4:1 (v/v)) to give tert-butyl (3-  
5 phenyl-1,2-dihydro-6-isoquinolinyl)methylcarbamate (0.14 g, 93%) as a colorless powder.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.00 (6H, d, J= 6.6 Hz), 1.39 (9H, s), 1.42 (9H, s), 2.15-2.35 (1H, m), 4.07 (2H, d, J= 7.4 Hz), 4.19 (2H, d, J= 6.6 Hz), 4.26 (2H, d, J= 6.6 Hz), 4.45  
10 (1H, br), 4.81 (1H, br), 6.81 (1H, d, J= 1.1 Hz), 7.20-7.30 (2H, m), 7.30-7.40 (1H, m), 7.45-7.55 (3H, m), 8.42 (1H, d, J= 8.0 Hz).

(2) 3,6-Bis(aminomethyl)-2-isobutyl-4-phenyl-1(2H)-isoquinolinone dihydrochloride (0.080 g, 76%) as  
15 colorless powder. [synthesized according to the method similar to that in Example 279 (3) from tert-butyl (3-  
-{[(tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)methylcarbamate (0.14 g, 0.26 mmol)]

20 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 0.91 (6H, d, J= 6.6 Hz), 1.95-2.20 (1H, m), 3.85 (2H, bs), 4.01 (2H, bs), 4.10 (2H, d, J= 6.6 Hz), 7.02 (1H, d, J= 1.0 Hz), 7.35-7.45 (2H, m), 7.50-7.60 (3H, m), 7.72 (1H, dm, J= 8.4 Hz), 8.36 (1H, d, J=8.4 Hz), 8.45 (3H, bs), 8.62 (3H, bs).

25 Melting point: 282-285°C

#### Example 290

3-(Aminomethyl)-2-isobutyl-4-phenyl-6-[5-(trifluoromethyl)-1H-1,2,4-triazol-3-yl]-1(2H)-isoquinolinone dihydrochloride

30 (1) A mixture of ethyl trifluoroacetate (0.038 mL, 0.31 mmol) and hydrazine monohydrate (0.026 mL, 0.50 mmol) in tetrahydrofuran (3 mL) was refluxed in a sealed tube for 1 h, the reaction was allowed to cool to room temperature. To the mixture were added tert-butyl {6-  
35 [amino(imino)methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl)methylcarbamate diacetate (0.14

g, 0.25 mmol) and sodium hydroxide (0.027 g, 0.55 mmol), and the resulting mixture was refluxed for 3 h. The reaction mixture was partitioned between water (10 mL) and ethyl acetate (30 mL). The organic layer was washed  
5 with water and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate= 3:1 (v/v)) to give tert-butyl {2-isobutyl-1-oxo-4-phenyl-6-[5-(trifluoromethyl)-1H-  
10 1,2,4-triazol-3-yl]-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.074 g, 55%) as a colorless powder.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.00 (6H, d, J= 6.6 Hz), 1.43 (9H, s), 2.10-2.35 (1H, m), 4.08 (2H, d, J= 7.4 Hz), 4.18 (2H, d, J= 5.2 Hz), 4.71 (1H, br), 7.20-7.30 (3H, m), 7.35-7.50  
15 (4H, m), 8.02 (1H, dd, J= 1.6, 8.6 Hz), 8.46 (1H, d, J= 8.6 Hz).

(2) 3-(Aminomethyl)-2-isobutyl-4-phenyl-6-[5-(trifluoromethyl)-1H-1,2,4-triazol-3-yl]-1(2H)-  
20 isoquinolinone dihydrochloride (0.063 g, 100%) as yellow crystals.

[synthesized according to the method similar to that in Example 279 (3) from tert-butyl {2-isobutyl-1-oxo-4-phenyl-6-[5-(trifluoromethyl)-1H-1,2,4-triazol-3-yl]-  
25 1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.065 g, 0.12 mmol)]

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 0.94 (6H, d, J= 6.6 Hz), 1.72 (1H, br), 2.05-2.20 (1H, m), 3.88 (2H, bs), 4.09 (2H, d, J= 7.2 Hz), 7.40-7.50 (2H, m), 7.55-7.70 (4H, m), 8.23 (1H, dd, J= 1.6, 8.4 Hz), 8.50 (3H, bs), 8.52 (1H, d, J= 8.4 Hz).

Melting point: 140-143°C

#### Example 291

3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-  
35 isoquinolinecarboxamide dihydrochloride

This compound was synthesized according to the method

similar to that in Example 279 (3) from tert-butyl {6-[amino(imino)methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl}methylcarbamate diacetate.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 0.92 (6H, d, J= 6.6 Hz), 2.00-2.20 (1H, m), 3.90 (2H, bs), 4.12 (2H, d, J= 7.0 Hz), 7.24 (1H, d, J= 1.6 Hz), 7.40-7.50 (2H, m), 7.50-7.65 (3H, m), 7.86 (1H, dd, J= 1.6, 8.4 Hz), 8.49 (1H, d, J=8.4 Hz), 8.69 (3H, bs), 9.26 (2H, bs), 9.52 (2H, bs).

Melting point: 171-173°C

10 **Example 292**

Methyl 2-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]-1H-imidazole-4-carboxylate dihydrochloride

- (1) To a mixture of tert-butyl {6-[amino(hydroxyimino)-methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinyl}methylcarbamate (0.47 g, 1.0 mmol) and triethylamine (0.17 mL, 1.2 mmol) in ethyl acetate (10 mL) was added methylpropionate (0.10 g, 1.2 mmol), and the mixture was stirred at room temperature for 17 h.
- 20 The reaction mixture was poured into water (5 mL), and the organic layer was separated. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. To the residue was added p-xylene (10 mL), the mixture was refluxed for 40 h. The
- 25 reaction mixture was diluted with ethyl acetate (100 mL), and the solution was washed with water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate= 1:1 (v/v)) to give methyl 2-(3-[(tert-butoxycarbonyl)amino]methyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)-1H-imidazole-4-carboxylate (0.22 g, 42%) as an orange powder.

- <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.98 (6H, d, J= 6.6 Hz), 1.53 (9H, s), 2.00-2.25 (1H, m), 3.87 (3H, s), 4.00-4.25 (4H, m), 6.37 (1H, br), 7.15-7.25 (1H, m), 7.25-7.55 (7H, m), 7.82 (1H,
- 35



dm, J= 8.4 Hz), 8.23 (1H, d, J= 8.4 Hz).

(2) A solution of methyl 2-(3-((tert-butoxycarbonyl)amino)methyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinoliny)-1H-imidazole-4-carboxylate  
5 (0.10 g, 0.19 mmol) in trifluoroacetic acid (3 mL) was stirred at room temperature for 5 min. The reaction mixture was concentrated, and purified by HPLC. The desired fractions were concentrated and then to the residue was added a 4N hydrogen chloride ethyl acetate  
10 solution (1 mL). The mixture was concentrated, and the residue was recrystallized from ethanol-ethyl acetate (10:1, v/v, 2 mL) to give methyl 2-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinoliny)-1H-imidazole-4-carboxylate dihydrochloride (0.050g, 53%) as  
15 a yellow powder.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 0.93 (6H, d, J= 6.6 Hz), 2.00-2.25 (1H, m), 3.77 (3H, s), 3.84 (2H, s), 4.08 (2H, d, J= 7.2 Hz), 7.40-7.50 (3H, m), 7.55-7.65 (4H, m), 7.90 (1H, s), 8.20 (1H, dd, J= 1.8, 8.4 Hz), 8.43 (1H, d, J= 8.4 Hz),  
20 8.51 (3H, bs).

Melting point: 266-270°C

#### Example 293

Ethyl 3-[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinoliny)-1,2,4-oxadiazole-5-carboxylate  
25 hydrochloride

(1) To a mixture of tert-butyl {6-[amino(hydroxyimino)methyl]-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinoliny)methylcarbamate (0.23 g, 0.50 mmol) and pyridine (0.043 mL, 0.53 mmol) in toluene  
30 (20 mL) was added ethyl chlorooxacetate (0.059 mL, 0.53 mmol), and the mixture was stirred at room temperature for 1 h and at 80°C for 1 h. The reaction mixture was partitioned between water (50 mL) and ethyl acetate (50 mL). The organic layer was washed with brine, dried over  
35 anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel

column chromatography (n-hexane:ethyl acetate= 20:1 -  
1:3 (v/v)) and recrystallized from diisopropyl ether-  
ethyl acetate (20:1, v/v, 5 mL) to give ethyl 3-(3-  
5 {[(tert-butoxycarbonyl)amino]methyl}-2-isobutyl-1-oxo-4-  
phenyl-1,2-dihydro-6-isoquinolinyl)-1,2,4-oxadiazole-5-  
carboxylate (0.13 g, 48%) as colorless crystals.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.02 (6H, d, J= 6.6 Hz), 1.43 (9H, s),  
1.47 (3H, t, J= 7.2 Hz), 2.15-2.35 (1H, m), 4.11 (2H, d,  
J= 7.2 Hz), 4.22 (2H, d, J= 5.6 Hz), 4.45-4.60 (1H, br),  
10 4.54 (2H, q, J= 7.2 Hz), 7.25-7.35 (2H, m), 7.50-7.60  
(3H, m), 7.74 (1H, d, J= 1.2 Hz), 8.17 (1H, dd, J= 1.2,  
8.4 Hz), 8.60 (1H, d, J= 8.4 Hz).

(2) A solution of ethyl 3-(3-[(tert-  
butoxycarbonyl)amino]methyl)-2-isobutyl-1-oxo-4-phenyl-  
15 1,2-dihydro-6-isoquinolinyl)-1,2,4-oxadiazole-5-  
carboxylate (0.070 g, 0.13 mmol) in trifluoroacetic acid  
(3 mL) was stirred at room temperature for 5 min. The  
reaction mixture was concentrated, and to the residue  
was added a solution of 4N hydrogen chloride in ethyl  
20 acetate (3 mL). The mixture was concentrated, and the  
residue was recrystallized from diisopropyl ether-ethyl  
acetate-methanol (15:40:1, v/v, 5 mL) to give ethyl 3-  
[3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-  
6-isoquinolinyl]-1,2,4-oxadiazole-5-carboxylate  
25 hydrochloride (0.061 g, 100%) as a colorless powder.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 0.94 (6H, d, J= 6.6 Hz), 1.34 (3H, t,  
J= 7.2 Hz), 2.00-2.20 (1H, m), 3.90 (2H, bs), 4.10 (2H,  
d, J= 5.0 Hz), 4.43 (2H, d, J= 7.2 Hz), 7.40-7.50 (2H,  
m), 7.55-7.70 (4H, m), 8.22 (1H, dd, J= 1.4, 8.4 Hz),  
30 8.30-8.60 (3H, br), 8.55 (1H, d, J= 8.4 Hz).

Melting point: 266-270°C

#### Reference Example 1

##### 2-Benzoyl-4-bromobenzoic acid

A mixture of benzene (2.94 ml), o-dichlorobenzene  
35 (20 ml) and aluminum chloride (5.87 g) was cooled to 5°C  
and 5-bromophthalic anhydride (5.0 g) was added by small

portions while maintaining the temperature of the mixture below 10°C. The mixture was stirred at around 25°C for 1 h and then at 80°C for 1 h. The reaction mixture was cooled to around 5°C and ethyl acetate (40 ml) was added dropwise. Water (20 ml) was added dropwise below 40°C. The organic layer was separated and 4N hydrochloric acid (20 ml) was added. The mixture was stirred until the precipitated solid was dissolved. The organic layer was separated and washed with water (20 ml). The solvent was evaporated and toluene (30 ml) and ethyl acetate (3 ml) were added to the residue, which was followed by heating to 80°C. The obtained solution was cooled to 25°C over 30 min and the precipitated crystals were collected by filtration. The crystals were dissolved in a mixture of toluene (30 ml) and ethyl acetate (1.5 ml) by heating and the obtained solution was cooled to 25°C and then to 5°C. The precipitated crystals were collected by filtration and washed with toluene to give the title compound (2.81 g, yield 41.8%).  
<sup>1</sup>H-NMR(300MHz, CDCl<sub>3</sub>) δ:7.41-7.46(2H, m), 7.51-7.60(2H, m), 7.69-7.72(3H, m), 7.94(1H, d, J=8.4Hz)

#### Reference Example 2

##### Isobutylaminoacetonitrile

To a mixture of isobutylamine (180.3 g), triethylamine (274.9 g) and ethyl acetate (900 ml) was added dropwise bromoacetonitrile (304.8 g) under ice-cooling below 30°C over about 2 h. The reaction mixture was adjusted to 25°C, stirred for 3 h and washed with water (900 ml) and 10% brine (900 ml). The solvent was evaporated and the obtained pale-yellow oil was distilled under reduced pressure. The bp<sub>10mmHg</sub> 82°C fractions were collected to give the title compound (198.3 g).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ:0.94(6H, d, J=6.6Hz), 1.17(1H, br), 1.74(1H, m), 2.54(2H, d, J=6.6Hz), 3.59(2H, s)

**Experimental Example 1****1) Preparation of dipeptidyl peptidase IV crude enzyme solution**

The enzyme activity of dipeptidyl peptidase IV  
5 present in human colonic adenocarcinoma-derived cell  
line Caco-2 cell membrane has been already reported by  
Yong S. Chung et al. (Cancer Research, vol. 45, pp. 2976-  
2982, 1985).

A dipeptidyl peptidase IV crude enzyme solution was  
10 prepared from culture cell of Caco-2 (ATCC HTB-37). The  
Caco-2 cells were cultured in D-MEM medium (manufactured  
by Nissui Pharmaceutical Co., Ltd.) containing 10% FBS  
(fetal calf serum (manufactured by GIBCO)). The cell  
extract was prepared by soaking the cells collected by  
15 removing the medium in 20 mM phosphate buffer (pH 7.5)  
containing 0.5% Triton X-100, extracting for 30 min in  
an ice bath and separating the supernatant obtained by  
centrifugation at 1500 g for 30 min. The cell extract  
(22 ml) was applied to a column of Sephadex G-200 (600  
20 ml, manufactured by Pharmacia Corporation) equilibrated  
with 20 mM Tris-hydrochloride buffer (pH 7.5) and  
eluted with the same buffer. The elution was  
fractionated by 10 ml, examined for enzyme activity and  
190 ml-280 ml fractions (90 ml) were collected. The  
25 same buffer (260 ml) was added for dilution to give a  
crude enzyme solution (14 mU/ml, 350 ml). One unit of  
the dipeptidyl peptidase IV enzyme activity was defined  
as an enzyme amount that produces 1  $\mu$ mol of p-  
nitroaniline from glycylprolyl-p-nitroanilide in 1 min.

**30 2) Determination of Caco-2-derived dipeptidyl peptidase  
IV inhibitory activity**

The reaction was carried out according to the  
method of Nagatsu et al. (Analytical Biochemistry, vol.  
74, pp. 466-467, 1976) using a 96 well flat-bottomed  
35 plate at 37°C.

An N,N-dimethylformamide solution (5  $\mu$ l) containing

the test compound was added to a mixture of water (25  $\mu$ l), 1M Tris-hydrochloride buffer (10  $\mu$ l, pH 7.5) and 1 mM aqueous glycyloprolyl-p-nitroanilide (Gly-Pro-p-NA; manufactured by Backem AG) solution (50  $\mu$ l) to prepare a mixed solution. The Caco-2-derived dipeptidyl peptidase IV crude enzyme solution (10  $\mu$ l) obtained in the aforementioned 1) was added to the above-mentioned mixed solution and the enzyme reaction was started at 37°C. The absorbance after 0 h and 3 h was measured using a microplate reader (Multiskan Bichromatic; manufactured by Labsystems) at a wavelength of 405 nm and an increase ( $\Delta$ ODs) was determined. At the same time, an increase ( $\Delta$ ODc) in absorbance of the reaction mixture without the test compound, and an increase ( $\Delta$ ODb) in absorbance of the reaction mixture without the test compound and the enzyme were determined and percent inhibition of dipeptidyl peptidase IV enzyme activity was calculated from the following formula:

$$\{1 - [(\Delta\text{ODs} - \Delta\text{ODb}) / (\Delta\text{ODc} - \Delta\text{ODb})]\} \times 100$$

The dipeptidyl peptidase IV inhibitory activity of the test compound group is expressed in  $\text{IC}_{50}$  value ( $\mu\text{M}$ ) and shown in Table 8.

Table 8

Test compound (Example No.)	$\text{IC}_{50}$ value ( $\mu\text{M}$ )
95	0.28
109	0.36
112	0.25

As shown above, the compound of the present invention has a superior dipeptidyl peptidase IV enzyme activity, and is useful as an agent for the prophylaxis or treatment of diabetes and the like.

**Experimental Example 2**

Determination of dipeptidyl peptidase IV inhibitory activity in rat plasma

The reaction was carried out according to the method of Raymond et al. (Diabetes, vol. 47, pp. 1253-1258, 1998) using a 96 well flat-bottomed plate at 30°C. An N,N-dimethylformamide solution (1 µl) containing the test compound was added to a mixture of water (69 µl), 1M Tris-hydrochloride buffer (10 µl, pH 7.5) and 1 mM aqueous Gly-Pro-p-NA solution (100 µl) to prepare a mixed solution. Plasma (20 µl) prepared from blood of SD rat by a conventional method was added the above-mentioned mixed solution and the enzyme reaction was started at 30°C. The absorbance after 0 h and 1 h was measured using a microplate reader at a wavelength of 405 nm and an increase ( $\Delta OD_s$ ) was determined. At the same time, an increase ( $\Delta OD_c$ ) in absorbance of the reaction mixture without the test compound, and an increase ( $\Delta OD_b$ ) in absorbance of the reaction mixture without the test compound and the enzyme were determined and percent inhibition of dipeptidyl peptidase IV enzyme activity was calculated from the following formula:

$$\{1 - [(\Delta OD_s - \Delta OD_b) / (\Delta OD_c - \Delta OD_b)]\} \times 100$$

The dipeptidyl peptidase IV inhibitory activity of the test compound group is expressed in  $IC_{50}$  value ( $\mu M$ ) and shown in Table 9.

Table 9

Test compound (Example No.)	$IC_{50}$ value ( $\mu M$ )
95	0.18
109	0.15
112	0.32

As shown above, the compound of the present invention has a superior dipeptidyl peptidase IV enzyme

activity, and is useful as an agent for the prophylaxis or treatment of diabetes and the like.

### Experimental Example 3

Plasma glucose-lowering effect and insulinotropic effect  
5 in rat.

Female Wistar fatty rats (17-week-old, 6 per group) were fasted overnight and blood was drawn from the tail vein. The plasma glucose level before administration of the test compound was measured. Then the test compound  
10 (3 mg/kg body weight/5 mL) suspended in 0.5% methyl cellulose was orally administered to the rats using a gastric tube. Oral glucose tolerance test (1 g/kg body weight/5 mL) was started 60 min later. Blood was drawn at 30 min after starting glucose load, and plasma  
15 glucose level and insulin level of the serum were measured. The plasma glucose level was measured using an automatic analyzer (HITACHI 7070) and the insulin level was measured using a radio immunoassay kit (trademark: SHIONORIA insulin kit (manufactured by  
20 Shionogi & Co., Ltd.)).

The plasma glucose level and insulin level of the test compound group are expressed in a value (%) relative to the control group and shown in Table 10.

25 Table 10

Test compound (Example No.)	Plasma glucose level (% of control)	insulin level (% of control)
95	82	188
109	73	205
112	76	255

As shown above, the compound of the present invention has a superior plasma glucose level-lowering  
30 effect and a superior insulinotropic effect, and is useful as an agent for the prophylaxis or treatment of diabetes and the like.

**Formulation Example 1 (production of capsule)**

	1) compound of Example 95	30 mg
	2) fine cellulose powder	10 mg
	3) lactose	19 mg
5	<u>4) magnesium stearate</u>	<u>1 mg</u>
	total	60 mg

1), 2), 3) and 4) are mixed and filled in gelatin capsules.

**Formulation Example 2 (production of tablet)**

10	1) compound of Example 95	30 g
	2) lactose	50 g
	3) corn starch	15 g
	4) calcium carboxymethylcellulose	44 g
	<u>5) magnesium stearate</u>	<u>1 g</u>
15	total of 1000 tablets	140 g

The entire amounts of 1), 2) and 3), and 30 g of 4) are kneaded with water, dried in vacuo and granulated. The granules are mixed with 14 g of 4) and 1 g of 5) and the mixture is compressed with a tableting machine, whereby 1000 tablets containing 30 mg of compound of Example 95 per tablet are obtained.

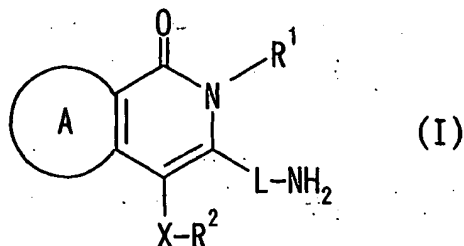
The compound and the pharmaceutical agent of the present invention show a superior peptidase (preferably dipeptidyl peptidase-IV)-inhibitory activity and are useful as an agent for the prophylaxis or treatment of diabetes and the like.

This application is based on patent application Nos. 2001-27349, 2001-292388 and 2001-382232 filed in Japan, the contents of which are hereby incorporated by reference. All of the references cited herein, including patents, patent applications and publications, are hereby incorporated in their entireties by reference.



## CLAIMS

1. A compound of the formula



5 wherein

ring A is an optionally substituted 5 to 10-membered aromatic ring;

$R^1$  and  $R^2$  are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

X is a bond, -O-, -S-, -SO-, -SO<sub>2</sub>- or -NR<sup>3</sup>- ( $R^3$  is a hydrogen atom or an optionally substituted hydrocarbon group); and

15 L is a divalent hydrocarbon group or a salt thereof, except 3-(aminomethyl)-2,6,7-trimethyl-4-phenyl-1(2H)-isoquinolinone, 3-(aminomethyl)-2-methyl-4-phenyl-1(2H)-isoquinolinone, 3-(aminomethyl)-6-chloro-2-methyl-4-phenyl-1(2H)-isoquinolinone and 3-(aminomethyl)-2-isopropyl-4-phenyl-1(2H)-isoquinolinone.

2. The compound of claim 1, wherein the 5 to 10-membered aromatic ring for ring A is a benzene ring.

3. The compound of claim 1, wherein the ring A is a 5 to 10-membered aromatic ring optionally having 1 to 3 substituent(s) selected from

a) a halogen atom,

b) a nitro group,

- c) a cyano group,
- d) a C<sub>1-3</sub> alkylenedioxy group,
- e) a C<sub>1-10</sub> alkyl group or a C<sub>2-10</sub> alkenyl group, each optionally having 1 to 3 substituent(s) selected from a
  - 5 halogen atom, a hydroxy group, a carboxyl group, an alkoxy carbonyl group having 2 to 8 carbon atoms, a carbamoyl group, a cyano group, an amino group, an alkanoylamino group having 2 to 8 carbon atoms, an alkoxy carbonylamino group having 2 to 8 carbon atoms, an
  - 10 alkylsulfonylamino group having 1 to 8 carbon atoms,
  - f) an optionally substituted hydroxy group,
  - g) an acyl group,
  - h) an optionally substituted amino group,
  - i) an aryl group having 6 to 14 carbon atoms,
  - 15 j) an optionally substituted thiol group, and
  - k) an optionally substituted heterocyclic group.

4. The compound of claim 1, wherein R<sup>1</sup> is an alkyl group having 1 to 10 carbon atom(s).

20

5. The compound of claim 1, wherein R<sup>1</sup> is an alkyl group having 4 to 10 carbon atoms.

6. The compound of claim 1, wherein X is a bond or -O-.

25

7. The compound of claim 1, wherein the divalent hydrocarbon group for L is an alkylene group having 1 to 10 carbon atom(s).

30 8. The compound of claim 1, wherein R<sup>2</sup> is an optionally substituted hydrocarbon group.

9. The compound of claim 1, wherein R<sup>2</sup> is an alkyl group having 1 to 10 carbon atom(s), an aryl group having 6 to  
35 14 carbon atoms or an aralkyl group having 7 to 13 carbon atoms, each optionally having 1 to 3

substituent(s) selected from halogen atom, hydroxy group, nitro group, amino group, optionally halogenated alkyl group having 1 to 6 carbon atom(s), alkoxy group having 1 to 6 carbon atom(s), aromatic heterocyclic group and  
5 cycloalkyl group having 3 to 10 carbon atoms.

10. The compound of claim 1, which is 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carbonitrile,  
10 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carboxylic acid,  
2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carboxamide,  
ethyl 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-  
15 dihydro-6-isoquinolyl]-1,3-thiazole-4-carboxylate,  
(E)-3-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-2-propenamide,  
(E)-3-[3-(aminomethyl)-2-isobutyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]-2-propenamide,  
20 3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxamide,  
2-[[3-(aminomethyl)-2-isobutyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]oxy]acetamide,  
or a salt thereof.

25 11. A crystal of 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carbonitrile or a salt thereof.

30 12. A crystal of 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carboxamide or a salt thereof.

13. A crystal of 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-  
35 1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carboxamide or a salt thereof.

14. A crystal of ethyl 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazole-4-carboxylate or a salt thereof.

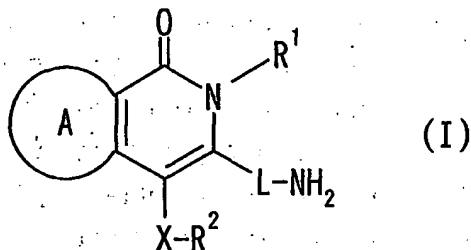
15. A crystal of (E)-3-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-2-propenamide or a salt thereof.

16. A crystal of (E)-3-[3-(aminomethyl)-2-isobutyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]-2-propenamide or a salt thereof.

17. A crystal of 3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxamide or a salt thereof.

18. A crystal of 2-[[3-(aminomethyl)-2-isobutyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]oxy]acetamide or a salt thereof.

19. A pharmaceutical agent containing a compound of the formula



wherein  
ring A

is an optionally substituted 5 to 10-membered aromatic ring;

R<sup>1</sup> and R<sup>2</sup>

are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic

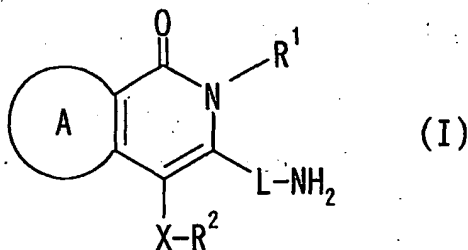
group;

X is a bond, -O-, -S-, -SO-, -SO<sub>2</sub>- or -NR<sup>3</sup>-  
(R<sup>3</sup> is a hydrogen atom or an optionally  
substituted hydrocarbon group); and

5 L is a divalent hydrocarbon group,  
or a salt thereof.

20. A pharmaceutical agent comprising the pharmaceutical  
agent of claim 19 in combination with at least one  
10 member selected from an insulin preparation, an insulin  
sensitizer, an  $\alpha$ -glucosidase inhibitor, a biguanide and  
an insulin secretagogue.

21. An agent for prophylaxis or treatment of diabetes,  
15 which contains a compound of the formula



wherein

ring A is an optionally substituted 5 to 10-  
membered aromatic ring;

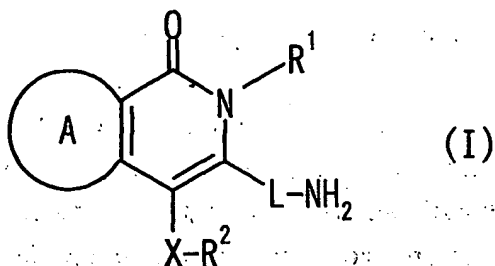
20 R<sup>1</sup> and R<sup>2</sup> are the same or different and each is an  
optionally substituted hydrocarbon group or  
an optionally substituted heterocyclic  
group;

X is a bond, -O-, -S-, -SO-, -SO<sub>2</sub>- or -NR<sup>3</sup>-  
25 (R<sup>3</sup> is a hydrogen atom or an optionally  
substituted hydrocarbon group); and

L is a divalent hydrocarbon group,  
a salt thereof or a prodrug thereof.

30 22. An agent for prophylaxis or treatment of diabetic

complications, which contains a compound of the formula



wherein

ring A

is an optionally substituted 5 to 10-membered aromatic ring;

R<sup>1</sup> and R<sup>2</sup>

are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

10 X

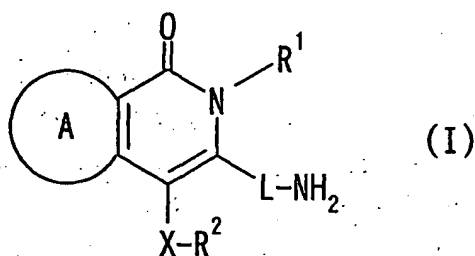
is a bond, -O-, -S-, -SO-, -SO<sub>2</sub>- or -NR<sup>3</sup>- (R<sup>3</sup> is a hydrogen atom or an optionally substituted hydrocarbon group); and

L

is a divalent hydrocarbon group, a salt thereof or a prodrug thereof.

15

23. An agent for prophylaxis or treatment of impaired glucose tolerance, which contains a compound of the formula



20 wherein

ring A

is an optionally substituted 5 to 10-membered aromatic ring;

R<sup>1</sup> and R<sup>2</sup>

are the same or different and each is an optionally substituted hydrocarbon group or

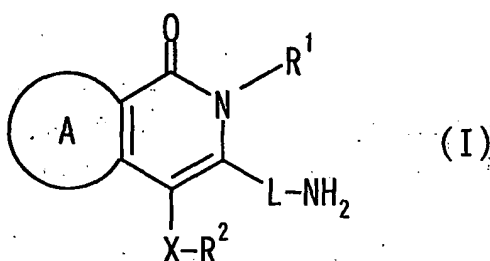
an optionally substituted heterocyclic group;

X is a bond, -O-, -S-, -SO-, -SO<sub>2</sub>- or -NR<sup>3</sup>-

(R<sup>3</sup> is a hydrogen atom or an optionally substituted hydrocarbon group); and

L is a divalent hydrocarbon group,  
a salt thereof or a prodrug thereof.

24. An agent for prophylaxis or treatment of obesity,  
which contains a compound of the formula



wherein

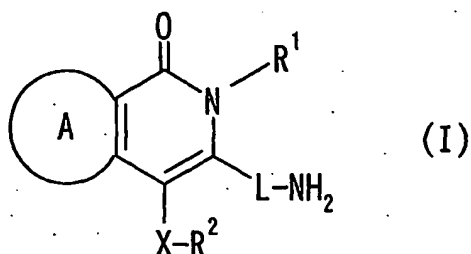
ring A is an optionally substituted 5 to 10-membered aromatic ring;

15 R<sup>1</sup> and R<sup>2</sup> are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

X is a bond, -O-, -S-, -SO-, -SO<sub>2</sub>- or -NR<sup>3</sup>-  
(R<sup>3</sup> is a hydrogen atom or an optionally substituted hydrocarbon group); and

L is a divalent hydrocarbon group,  
a salt thereof or a prodrug thereof.

25 25. A peptidase inhibitor containing a compound of the formula



wherein

ring A is an optionally substituted 5 to 10-membered aromatic ring;

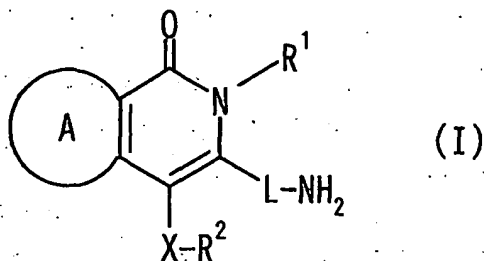
5  $R^1$  and  $R^2$  are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

X is a bond, -O-, -S-, -SO-, -SO<sub>2</sub>- or -NR<sup>3</sup>-  
 10 ( $R^3$  is a hydrogen atom or an optionally substituted hydrocarbon group); and

L is a divalent hydrocarbon group,  
 a salt thereof or a prodrug thereof.

15 26. The inhibitor of claim 25, wherein the peptidase is dipeptidyl dipeptidase IV.

27. A method of prophylaxis or treatment of diabetes in a mammal, which method comprising administering a  
 20 compound of the formula



wherein

ring A is an optionally substituted 5 to 10-membered aromatic ring;



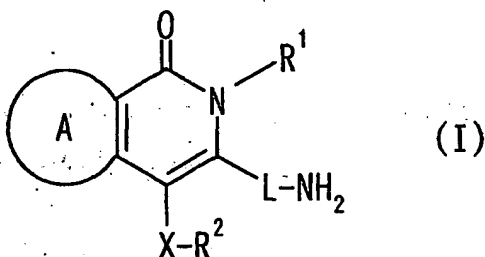
$R^1$  and  $R^2$  are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

5 X is a bond, -O-, -S-, -SO-, -SO<sub>2</sub>- or -NR<sup>3</sup>- ( $R^3$  is a hydrogen atom or an optionally substituted hydrocarbon group); and

L is a divalent hydrocarbon group,  
a salt thereof or a prodrug thereof to the mammal.

10

28. A method of prophylaxis or treatment of diabetic complications in a mammal, which method comprising administering a compound of the formula



15 wherein

ring A is an optionally substituted 5 to 10-membered aromatic ring;

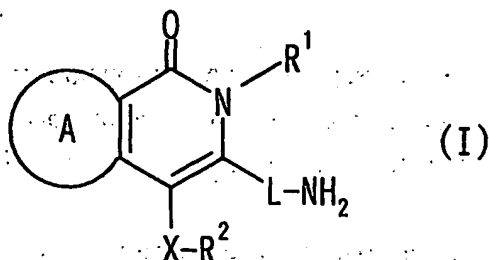
$R^1$  and  $R^2$  are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

20

X is a bond, -O-, -S-, -SO-, -SO<sub>2</sub>- or -NR<sup>3</sup>- ( $R^3$  is a hydrogen atom or an optionally substituted hydrocarbon group); and

25 L is a divalent hydrocarbon group,  
a salt thereof or a prodrug thereof to the mammal.

29. A method of prophylaxis or treatment of impaired glucose tolerance in a mammal, which method comprising  
30 administering a compound of the formula



wherein

ring A

is an optionally substituted 5 to 10-membered aromatic ring;

5 R<sup>1</sup> and R<sup>2</sup>

are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

X

is a bond, -O-, -S-, -SO-, -SO<sub>2</sub>- or -NR<sup>3</sup>-

10

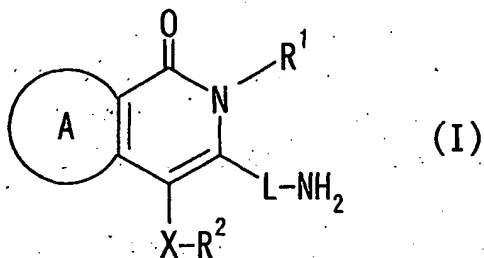
(R<sup>3</sup> is a hydrogen atom or an optionally substituted hydrocarbon group); and

L

is a divalent hydrocarbon group,

a salt thereof or a prodrug thereof to the mammal.

- 15 30. A method of prophylaxis or treatment of obesity in a mammal, which method comprising administering a compound of the formula



wherein

20 ring A

is an optionally substituted 5 to 10-membered aromatic ring;

R<sup>1</sup> and R<sup>2</sup>

are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic

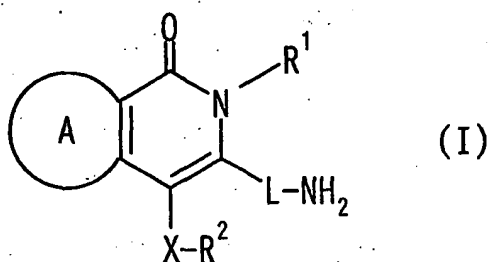
group;

X is a bond, -O-, -S-, -SO-, -SO<sub>2</sub>- or -NR<sup>3</sup>-  
(R<sup>3</sup> is a hydrogen atom or an optionally  
substituted hydrocarbon group); and

5 L is a divalent hydrocarbon group,  
a salt thereof or a prodrug thereof to the mammal.

31. A method of inhibiting peptidase in a mammal, which  
method comprising administering a compound of the

10 formula



wherein

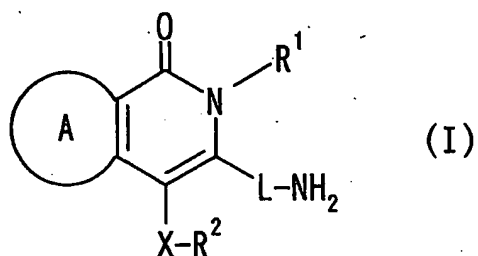
ring A is an optionally substituted 5 to 10-  
membered aromatic ring;

15 R<sup>1</sup> and R<sup>2</sup> are the same or different and each is an  
optionally substituted hydrocarbon group or  
an optionally substituted heterocyclic  
group;

X is a bond, -O-, -S-, -SO-, -SO<sub>2</sub>- or -NR<sup>3</sup>-  
20 (R<sup>3</sup> is a hydrogen atom or an optionally  
substituted hydrocarbon group); and

L is a divalent hydrocarbon group,  
a salt thereof or a prodrug thereof to the mammal.

25 32. Use of a compound of the formula



wherein

ring A

is an optionally substituted 5 to 10-membered aromatic ring;

5 R<sup>1</sup> and R<sup>2</sup>

are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

X

is a bond, -O-, -S-, -SO-, -SO<sub>2</sub>- or -NR<sup>3</sup>-

10

(R<sup>3</sup> is a hydrogen atom or an optionally substituted hydrocarbon group); and

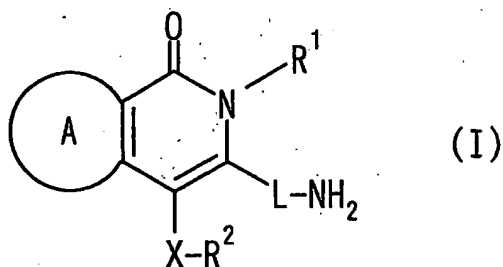
L

is a divalent hydrocarbon group,

a salt thereof or a prodrug thereof for production of an agent for prophylaxis or treatment of diabetes.

15

33. Use of a compound of the formula



wherein

ring A

is an optionally substituted 5 to 10-membered aromatic ring;

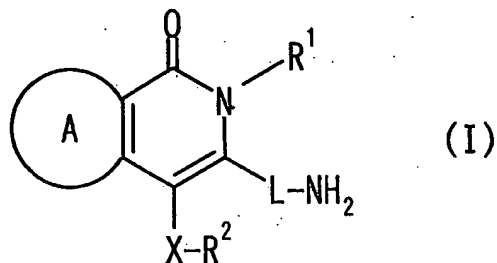
20

R<sup>1</sup> and R<sup>2</sup>

are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

X is a bond, -O-, -S-, -SO-, -SO<sub>2</sub>- or -NR<sup>3</sup>-  
 (R<sup>3</sup> is a hydrogen atom or an optionally  
 substituted hydrocarbon group); and  
 L is a divalent hydrocarbon group,  
 5 a salt thereof or a prodrug thereof for production of an  
 agent for prophylaxis or treatment of diabetic  
 complications.

34. Use of a compound of the formula



10

wherein

ring A

is an optionally substituted 5 to 10-  
 membered aromatic ring;

R<sup>1</sup> and R<sup>2</sup>

are the same or different and each is an  
 15 optionally substituted hydrocarbon group or  
 an optionally substituted heterocyclic  
 group;

X

is a bond, -O-, -S-, -SO-, -SO<sub>2</sub>- or -NR<sup>3</sup>-  
 (R<sup>3</sup> is a hydrogen atom or an optionally  
 20 substituted hydrocarbon group); and

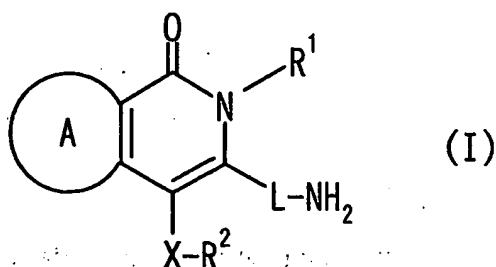
L

is a divalent hydrocarbon group,

a salt thereof or a prodrug thereof for production of an  
 agent for prophylaxis or treatment of impaired glucose  
 tolerance.

25

35. Use of a compound of the formula



wherein

ring A

is an optionally substituted 5 to 10-membered aromatic ring;

5 R<sup>1</sup> and R<sup>2</sup>

are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

X

is a bond, -O-, -S-, -SO-, -SO<sub>2</sub>- or -NR<sup>3</sup>-

10

(R<sup>3</sup> is a hydrogen atom or an optionally substituted hydrocarbon group); and

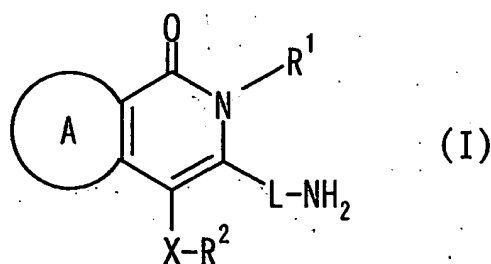
L

is a divalent hydrocarbon group,

a salt thereof or a prodrug thereof for production of an agent for prophylaxis or treatment of obesity.

15

36. Use of a compound of the formula



wherein

ring A

is an optionally substituted 5 to 10-membered aromatic ring;

20

R<sup>1</sup> and R<sup>2</sup>

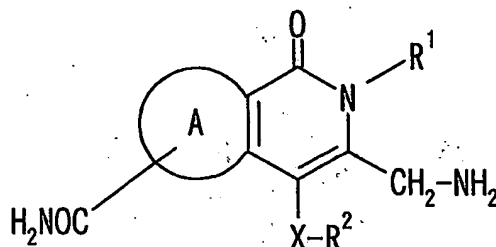
are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

X is a bond, -O-, -S-, -SO-, -SO<sub>2</sub>- or -NR<sup>3</sup>-  
(R<sup>3</sup> is a hydrogen atom or an optionally substituted hydrocarbon group); and

L is a divalent hydrocarbon group,

5 a salt thereof or a prodrug thereof for production of a peptidase inhibitor.

37. A production method of a compound of the formula



10 wherein

ring A

R<sup>1</sup> and R<sup>2</sup>

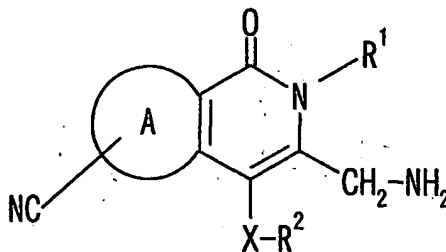
is a 5 to 10-membered aromatic ring;  
are the same or different and each is an  
optionally substituted hydrocarbon group or  
an optionally substituted heterocyclic  
15 group;

and

X

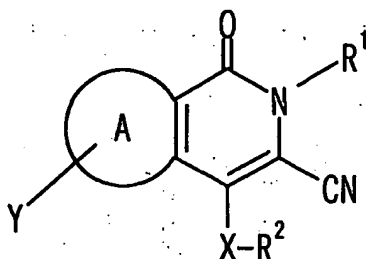
is a bond, -O-, -S-, -SO-, -SO<sub>2</sub>- or -NR<sup>3</sup>-  
(R<sup>3</sup> is a hydrogen atom or an optionally substituted hydrocarbon group),

20 or a salt thereof, which method comprises subjecting a compound of the formula



wherein the symbols are as defined above, or a salt thereof, to hydrolysis.

38. A compound of the formula

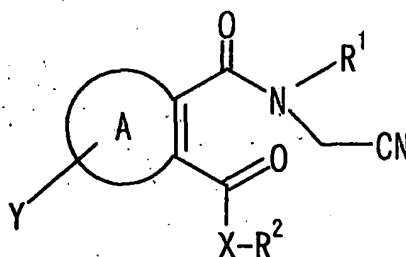


wherein

- 5 ring A is a 5 to 10-membered aromatic ring;  
 R¹ and R² are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;  
 10 X is a bond, -O-, -S-, -SO-, -SO₂- or -NR³- (R³ is a hydrogen atom or an optionally substituted hydrocarbon group); and  
 Y is a halogen atom, or a salt thereof.

15

39. A compound of the formula



wherein

- ring A is a 5 to 10-membered aromatic ring;  
 20 R¹ and R² are the same or different and each is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;  
 X is a bond, -O-, -S-, -SO-, -SO₂- or -NR³-



(R<sup>3</sup> is a hydrogen atom or an optionally substituted hydrocarbon group); and  
Y is a halogen atom,  
or a salt thereof.

5

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 02/00831

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 7 C07D217/24 A61K31/472 C07D401/12 A61K31/4725 C07D401/06 C07D417/06 C07D405/06 C07D495/04 A61K31/4365 C07D413/04 C07D401/04 C07D417/04 //(C07D495/04,333:00,221:00) According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D A61K Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the International search (name of data base and, where practical, search terms used) WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data, EPO-Internal		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	K.UNVERFERTH: "Synthese und antikonvulsive Aktivität von 3-Carbamoyl-4-aryl-isochinolin-1(2H)-onen" ARCHIV DER PHARMAZIE, vol. 324, no. 10, 1991, pages 809-814, XP001070958 cited in the application	38,39
A	see table 2, 6n,6o,6p and 2->3 and compound 9	1-37
X	DD 287 032 A (UNIV LEIPZIG) 14 February 1991 (1991-02-14) see claim 1, formula IV and formula V -/-	38,39
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
Date of the actual completion of the international search 10 May 2002		Date of mailing of the international search report 29/05/2002
Name and mailing address of the ISA European Patent Office, P.B. 6818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016		Authorized officer Scruton-Evans, I

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 02/00831

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	<p>WO 02 24655 A (MERCK &amp; CO INC ;CLAREMON DAVID A (US); LIVERTON NIGEL J (US); MCIN) 28 March 2002 (2002-03-28)</p> <p>see main formula, especially definition of Q and R4,R4' and compounds 33,37,36,29, page 70,39 page 34,114 page 65, 41 page 35 and the compounds 112 and 113 and reaction c, page 42</p>	1-9,19
Y	<p>EP 0 634 402 A (TAKEDA CHEMICAL INDUSTRIES LTD) 18 January 1995 (1995-01-18)</p> <p>cited in the application</p> <p>see excluded compounds ref examples 4,5 and 6 and also general formula page 19, definitions of W, S-2 and S-5</p>	1-37
Y	<p>IKEURA Y ET AL: "POTENT NK1 RECEPTOR ANTAGONISTS: SYNTHESIS AND ANTAGONISTIC ACTIVITY OF VARIOUS HETEROCYCLES WITH AN N-3,5-BIS(TRIFLUOROMETHYL)BENZYL-N-METHYLCARBAMOYL SUBSTITUENT"</p> <p>CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP,</p> <p>vol. 45, no. 10, 1997, pages 1642-1652, XP000910111</p> <p>ISSN: 0009-2363</p> <p>see compounds 10d,12d</p>	38,39
Y	<p>NATSUGARI H ET AL: "NOVEL, POTENT, AND ORALLY ACTIVE SUBSTANCE P ANTAGONISTS: SYNTHESIS AND ANTAGONIST ACTIVITY OF N-BENZYL CARBOXAMIDE DERIVATIVES OF PYRIDO[3,4-B]PYRIDINE"</p> <p>JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US,</p> <p>vol. 38, 1995, pages 3106-3120, XP002925569</p> <p>ISSN: 0022-2623</p> <p>see compounds 8,9</p>	38,39
A	<p>WO 98 38168 A (TANABE SEIYAKU CO ;IKEO TOMIHIRO (JP); OMORI KENJI (JP); UKITA TAT) 3 September 1998 (1998-09-03)</p> <p>the whole document</p>	1-37
A	<p>EP 0 585 913 A (TAKEDA CHEMICAL INDUSTRIES LTD) 9 March 1994 (1994-03-09)</p> <p>see also page 39, compounds XV,XVI</p> <p>the whole document</p>	1-39
A	<p>WO 98 18763 A (ASAI YASUYUKI;TANABE SEIYAKU CO ; OHNOKI TETSUO (JP); TANAKA SUMIK) 7 May 1998 (1998-05-07)</p> <p>the whole document</p>	1-39

-/-

# INTERNATIONAL SEARCH REPORT

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>US 6 090 786 A (BORLOO MARIANNE JEAN FRIEDA ET AL) 18 July 2000 (2000-07-18)  see Table 1, line 27  the whole document</p>	1-37

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Information on patent family members

International Application No

PCT/JP 02/00831

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			EP 0764151 A2	26-03-1997

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